VOLUME 52 NUMBER 6 JUNE 1959

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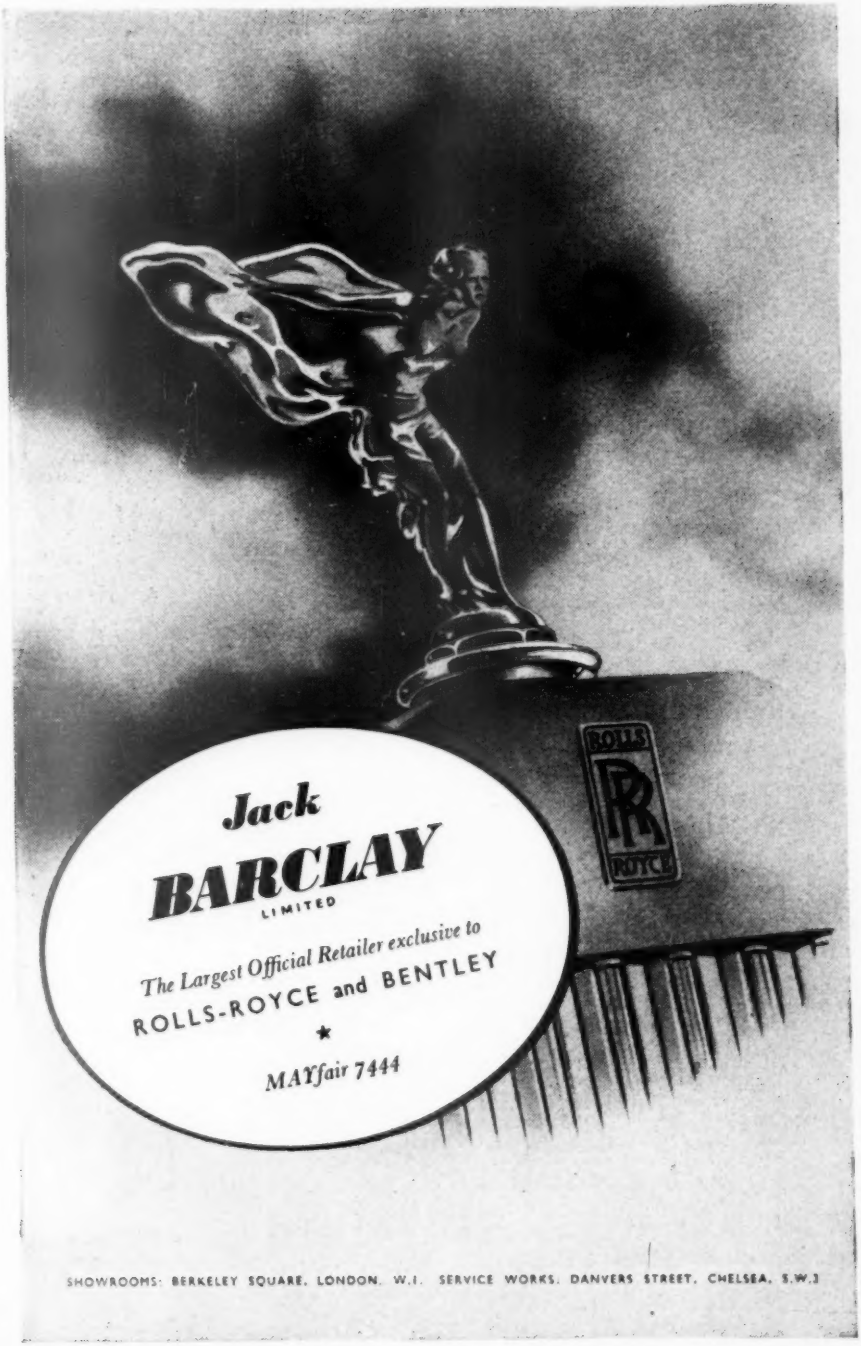

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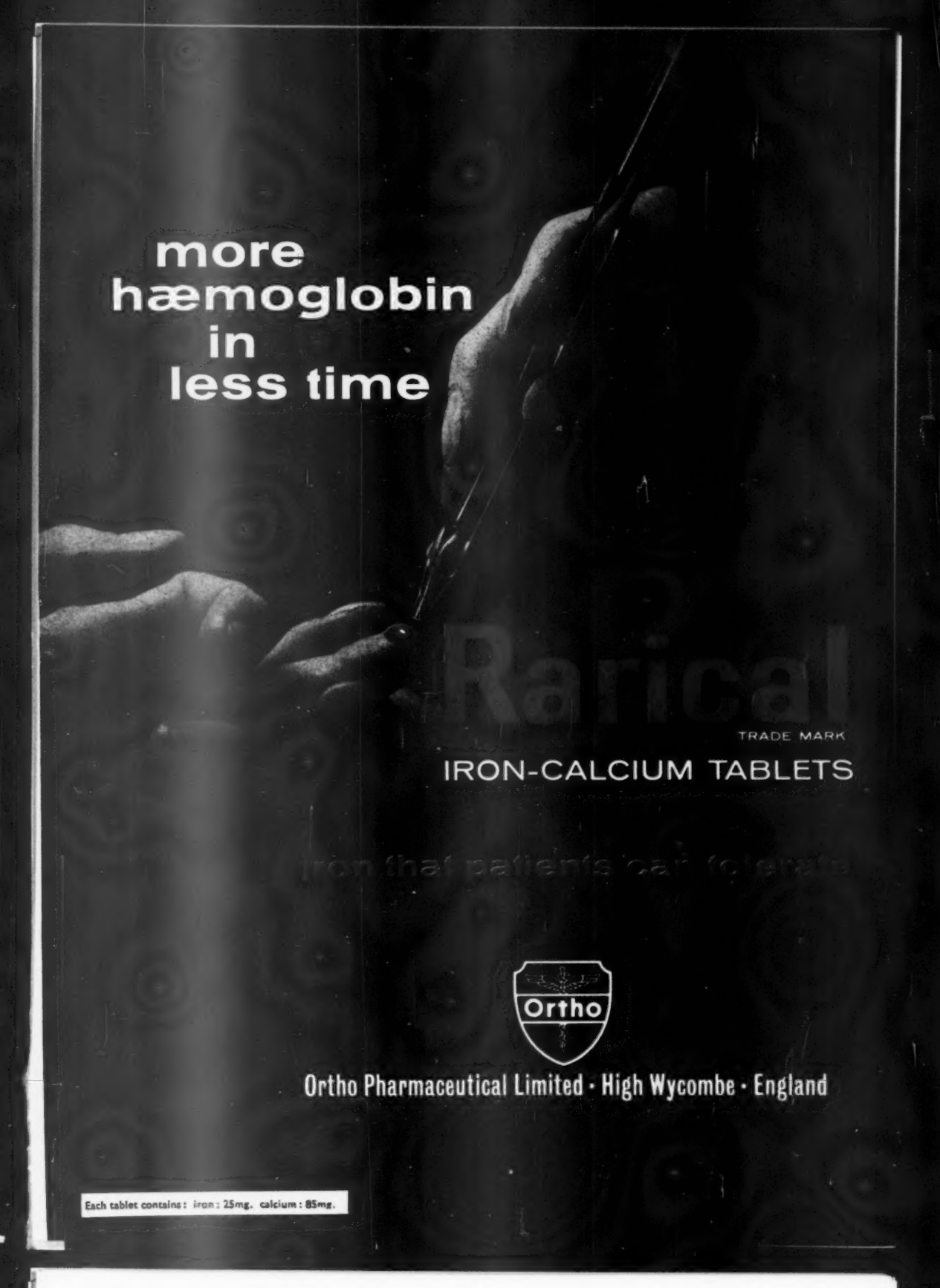
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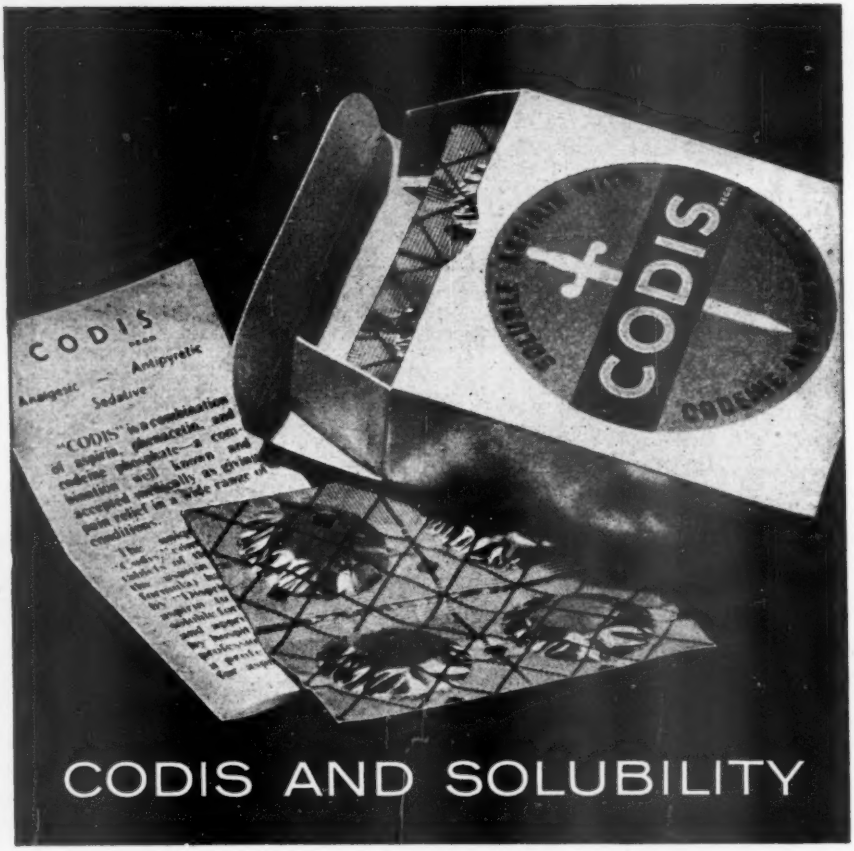

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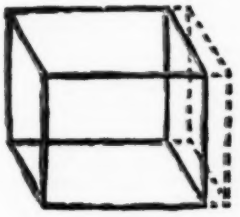

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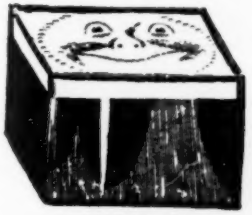

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HUGHLINGS JACKSON LECTURE

Excitation and Inhibition in Epilepsy

By Sir CHARLES SYMONDS, K.B.E., M.D.

London

ADMIRABLE in Hughlings Jackson's papers is his pithy way of telling a clinical story with running commentary of interjection and footnote. In his Lumleian Lectures (Jackson, 1931) he presents a case of local epilepsy in what he calls a drama of four acts. In the opening scene "A man, B., was seemingly quite well when he arrived at my house after a walk of about a mile." In the second act a fit begins in the toes of the left foot. Of the first act Jackson remarks: "The patient was not really well when he arrived at my house. He had a persistent discharging lesion, presumably in a few cells of his leg centre; so to say, he always carried it about with him, or, to speak more precisely, it was a persistent, quasi-parasitical, hyperfunctionable part of himself." This was indeed what he meant. Elsewhere he says: "The discharging lesion is a local, persisting, hyperphysiological state of nerve cells induced by some pathological change", and again, "These discharges are to be looked upon as gross exaggerations of healthy nervous discharges". As to the form this exaggeration might take he remarks in a later paper "I do not mean that 'nerve impulses' after discharges which produce convulsion travel faster than those after discharges of health, but that in the former case more numerous 'nerve impulses' are emitted in a given time, or else that more nerve cells are simultaneously discharging". Translated into terms of electrically recorded potentials these hypotheses are now seen to be correct, which is an indication both of Hughlings Jackson's imaginative genius and of his influence upon the form of neurophysiology as we know it to-day.

There are many questions about epilepsy to which there is still no satisfactory answer. What is the basis of the persistent discharging lesion such as Jackson's patient carried about with him? I do not, of course, mean to ask whether the patient had a tumour or a scar, but how such a tumour or scar causes a liability to seizures. Again, what is it that determines the onset of a seizure in a person carrying this liability? And once the seizure has begun what determines its cessation? To all these questions Jackson, and many others who have followed him, have devoted a great deal of thought yet they are perhaps worth reconsideration at the present time in the light of recent physiological and biochemical research. Setting aside the first question for the moment, let us consider what clinical observation may have to tell us about the excitation or inhibition of seizures.

CLINICAL OBSERVATION

The observation that in some cases an epileptic seizure might be provoked by physiological or psychical stimuli is an old one. Evoked seizures —a better term than reflex epilepsy—were recognized by Jackson (1925) and fully described by Gowers (1901). An excellent account of the subject is given by Allen (1945). I have found them described in 65 out of 1,000 consecutive patients presenting in my consulting-room with the complaint of epileptic seizures, but am convinced from retrospective analysis that other examples might have been discovered by proper enquiry. Precipitation by a particular stimulus in certain cases may be observed only in a small proportion of the seizures and may be omitted from the story, and in some instances the nature of the stimulus is such that it may easily escape notice. This until a few years ago was true for flickering light, now recognized as a common precipitant of *petit mal*. The element of flicker is, however, not essential and abrupt transition from darkness to light may evoke a seizure. The converse may also obtain. Two of my patients had attacks with a sudden change from light to darkness, as when entering a cinema. One of these almost always had a minor seizure within a second or two of closing her eyes when going to sleep, and her clothes had to be made especially loose to prevent exposure to darkness when dressing or undressing. It is evident, therefore, that the "off" as well as the "on" signal from the retina may be effective. This

may also be true for hearing. In one of my cases there was a particular liability for seizures to occur at moments of sudden transition from noise to unexpected silence.

It is well known that the visual or auditory stimulation required to excite a seizure may be of a complex kind. The act of reading provides a striking example and was clearly described by two of my patients, though it is only in the past three years that "reading epilepsy" has become widely recognized (Bickford *et al.*, 1956; Chavany *et al.*, 1956; Bingel, 1957; Stevens, 1957). In one of my patients writing was said to cause attacks, and I was able to witness a seizure thus precipitated. A comparable case was recorded by Gordon (1928). On the auditory side musicogenic epilepsy has long been known (Critchley, 1937), and there are other complex variants.

There are also cases in which a particular movement may evoke seizures, especially, as Gowers noted, movement after rest—getting out of a chair quickly or turning over in bed.

Precipitation of attacks by visceral stimuli is, I suspect, more common than has generally been supposed. When the association is constant it is easily recognized. For example, a man who had occasional major attacks in his sleep was also liable to minor seizures in the day, taking the form of sudden confusion and a sense of familiarity lasting two or three minutes. These never occurred except when he was eating and only towards the end of a heavy meal. The bigger the meal and the more quickly it was eaten the more likely he was to have an attack. Having become aware of this, he took care to avoid gastric distension and was thus able to avoid attacks, but on a recent occasion was obliged to eat a rushed meal, got a feeling of gastric distension and was unable to bring up wind (a procedure which had been previously effective in preventing an attack). He then had the usual aura, this time followed by a major seizure. Another patient also had his minor attacks only when eating and only after he had eaten a good deal. "If", he said, "I eat slowly and read they never happen." A comparable case is recorded by Allen (1945). Working backwards from these cases in which the association was invariable I have noted others in which attacks have occurred more often during meals than appeared likely from coincidence. Such observations illustrate the complex nature of the effective stimulus in certain cases and the consequent need for close interrogation before it is decided that there is no precipitating cause for epileptic seizures.

I shall refer only in passing to other and well-known stimuli that may evoke seizures—startle, sudden noise, painful or tactile stimulation, or a burst of anger, for example. It is also recognized that the evocation of seizures may be conditioned as in the case of a patient who learned to produce attacks in himself by looking at a safety-pin (Mitchell *et al.*, 1954).

In some cases of evoked epilepsy the activity or stimulation is effective only if prolonged for some time. Reading epilepsy is one example. The seizure does not occur when reading is begun but only after several minutes and sometimes only after two or three hours. Auditory stimulation also may need to be repeated or prolonged to evoke seizures. Critchley (1937) records a case in which attacks would develop if the patient heard a noise of a continued or monotonous order, such as machinery in a workshop or a kettle on the boil, and in one of my own patients reiterative noise such as a frog croaking or a cat mewing would precipitate seizures. In both instances the auditory stimulus had to continue for some time before the fit developed. The prolonged exercise of a particular mental activity may also be responsible. Playing chess in one of my patients and adding figures in another were very likely to end in an attack. In a case reported by Bingel (1957) seizures occurred after playing cards for any time longer than two hours.

That a chronic state of peripheral excitation may cause an increased liability to seizures appeared true in a patient who proved to have a right parasagittal meningioma. Twenty-three years before the onset of his seizures his left leg had been amputated below the knee. The attacks at first took the form of clonic twitching limited to the muscles of the stump, lasting a minute or two, and continued thus at the rate of one every two or three days for a year. The seizures then gradually altered in that the twitching would extend at first to the thigh, then to the abdomen and finally to the arm, and eventually he had an attack in which he lost his senses. During the two years in which he had been subject to the minor attacks he had accepted the opinion that his symptoms were due to irritation in the stump, though he himself had not been aware of any new or abnormal sensation in it. He had therefore removed his artificial limb whenever convenient during the day as well as at night, and had never experienced a seizure when it was off. I have assumed in this case that afferent impulses, which were always present but of which he was unaware, and which on arrival at his cortex had no effect under normal conditions, were a contributory cause of epileptic seizures when the tumour was present. If we assume that of all the afferent stimuli reaching the brain only a comparatively small fraction are perceived, the number of cases in which seizures

may be observed by the subject to be evoked by stimulation may be significant.

The arrest of a seizure after it has begun by means of some mental or bodily activity or a particular stimulus must be assigned to an inhibitory process. It has been many times described and in its simplest form is not uncommon. I have found it recorded in 53 out of the 1,000 cases already mentioned. In 25 instances it was stated that the attack could at times be cut short by some kind of mental effort. Most of these patients could not describe the occurrence better than to say that by pulling themselves together or by an effort of concentration they were able to snap out of it. But in 8 cases a description was volunteered of a deliberate switch of mental attention. For example, one patient with an aura of noise said "I may at this stage be able to jump my thoughts about and stop it". Another, whose attacks began with a sudden faraway feeling, a nice sort of feeling, said "If I don't think about it it's all right, but if I say 'Oh, Oh, look out, be careful' my mind automatically goes that way and I'm out". A patient who was himself a doctor and recognized his minor seizures, which consisted of a sudden feeling at the back of the nose going on to a disturbance of thought, stated "By an effort of concentration I can always fight it off, but on one occasion I thought 'How will it develop?' and at once lost my senses". On this occasion he had a major seizure.

The arrest of focal seizures by local stimulation of some kind was described by 12 of my patients and is so well known that the symptoms need not be described in detail.

The inhibitory process involved in arrest of seizures may be subject to the establishment of conditioned reflexes as in the remarkable case described by Efron (1956, 1957).

Physiology

Although it is now more than twenty years old the observation of self-sustained after-discharge of electric potentials in the cortex following electrical stimulation deserves first consideration, for the pattern and sequence of events correspond closely with those observed in a convulsive seizure, whether excited electrically or occurring as the result of disease. Cortical after-discharge following electrical stimulation, therefore, may be regarded as the counterpart of a subclinical seizure. Of especial interest is the manner in which the after-discharge ceases. Having continued for a time at a regular frequency of about 10 to 14 per second, the spikes then grow larger, and appear in groups with pauses in between. These pauses become gradually longer, up to half a second or more, until the after-discharge ceases. Following this, if the potentials of the after-discharge have been very large, the whole area may be left inexcitable as well as inactive for 10 to 20 seconds. These observations are quoted from the classic paper of Adrian (1936), suggesting in his words "a conflict between a process by which each wave makes the system more unstable and an opposing process which causes a slower and slower recovery and ultimately stops all activity for many seconds". This process, he remarked, might be an inhibition, an accumulation of waste products or an exhaustion of active material, "though if it is an exhaustion it must be one which affects every neurone—even those which have only come into action at the height of the after-discharge". This objection to the hypothesis of exhaustion has never been answered. No evidence has been brought forward to sustain the hypothesis of waste products. The possibility of an inhibitory process remains and has received some support from the observations of Rosenblueth and Cannon (1942). If the state of inexcitability and inactivity immediately following the cessation of discharge represents inhibition it is inhibition of a degree which is not found under normal conditions, and we may deduce that an abnormal state of excitation has in its turn evoked an abnormal state of inhibition.

We must next consider the observations of Eccles (1957) and his collaborators, derived from recording with the micro-electrode the potentials within single motoneurones. They have demonstrated two different types of potential, the excitatory post-synaptic potential (E.P.S.P.) and the inhibitory post-synaptic potential (I.P.S.P.), each obtained by an appropriate mode of peripheral stimulation. These potentials result from the flux of ions across the cell membrane, the flow being governed by changes in the permeability of the membrane, which again are determined by the effect upon the membrane of excitatory and inhibitory transmitter substances. The change of potential, therefore, whether a depolarization (E.P.S.P.) or a hyperpolarization (I.P.S.P.) records in electrical terms the culmination of a series of chemical events. Arising from these and related studies there are several observations of especial interest to the student of epilepsy. The first is the discovery that within the spinal cord the motoneurone gives off a collateral branch forming a synapse with a Renshaw cell, which in turn makes synaptic connexions with motoneurones. It has been demonstrated that the function of the Renshaw neuron is strictly inhibitory. Thus each time the motoneurone develops an axon potential it excites an inhibitory impulse to motoneurones. Excitation evokes inhibition.

Phillips (1956) has applied the micro-electrode method to Betz cells in the cat and has discovered waves of hyperpolarization occurring not only as a sequel of excitatory activity in the cell but as independent happenings. He has further shown (Phillips, 1959) that inhibitory as well as excitatory effects can be produced in a Betz cell by antidromic stimulation of pyramidal fibres in the medulla other than the axon of the cell under observation by the micro-electrode. He has referred in this connexion to the long-established anatomical observation that the Betz cells give rise to axon collaterals ending on short interneurones which form synapses with Betz cells, an arrangement so like that of the axon collateral of the motoneurone to the Renshaw cell that it seems possible that, as in the spinal cord so in the cortex, the motor cell each time it discharges an axon potential excites an inhibitory interneurone to discharge a volley of impulses aimed at itself and its neighbours—a feedback system, which, as Phillips remarks, would be important in tending to prevent convulsive activity.

If we assume that there are inhibitory neurones in the cortex the recent observations of Eccles (1957) and his collaborators on the action of strychnine upon the motoneurone become important in relation to the effect of this substance in producing focal epileptic activity when applied to the cortex. These workers have shown that strychnine has no direct effect upon the excitatory post-synaptic potential of the motoneurone in reflex excitation, but causes a great diminution of the expected inhibitory post-synaptic potential provoked by an appropriate stimulus. Eccles suggests that strychnine acts by competing with the inhibitory transmitter substance for the appropriate receptor patches on the sub-synaptic membrane, and speaks of it as the curare of the inhibitory synapse. If this should be true for cortical cells we should have the answers to a number of questions, but at the same time further questions to be answered. If the epileptic activity produced by strychnine is caused by a defect of inhibition whence comes the excitation? It may arise from afferent stimuli which would under normal conditions be inhibited and then have no electrical or clinical effect. It was long ago observed that if strychnine was applied to the motor cortex in a weak enough solution and for a short enough time convulsive activity was absent, but could be evoked by a sensory stimulus aimed at the appropriate area of cortex. Another answer to the same question might be that the resting activity of cortical cells may amount to convulsive activity when the inhibitory brakes are out of action. The effect of strychnine, on this hypothesis, would be satisfying for the clinician in that it offers the possibility of a persistent discharging lesion in the Jacksonian sense, which may be clinically subliminal except when some combination of stimuli, in space and time, evokes local excitation, stimuli of a kind and degree that would have caused no perceptible effect had it not been for the absence of inhibitory tone.

Relevant to the excitation of seizures by sensory stimuli are observations arising from the question raised by Adrian (1954) whether the afferent messages which can evoke sensation are allowed at all times to reach the cerebral cortex or are sometimes blocked at a lower level. There is now evidence recently reviewed by Dawson (1958) suggesting the existence of tonic activity descending from the cortex, and probably from the brain-stem and cerebellum, having an inhibitory effect at synapses on the afferent pathways. If it is accepted that the afferent inflow to the cortex is thus subject to continuous inhibitory control what might happen if this control were withdrawn? Dawson (1947) had previously observed, in certain patients subject to myoclonic seizures which could be provoked by sensory stimulation, that a sensory stimulus applied to the periphery led to an electrical response recorded from the scalp over the sensory area which was many times larger than that found in healthy people. These observations raise the possibility that depression of inhibitory control resulting from cerebral disease might cause a pathological increase in the size of an afferent volley, which in its turn could be a factor in the excitation of epileptic discharge. Further studies on the unanæsthetized cat by means of implanted electrodes (Hernandez-Peón *et al.*, 1957) suggest that inhibition of afferent inflow may be selective, and its direction governed by attention, so that, for example, impulses set up in the visual pathways by photic stimulation are depressed when the animal is at the same time exposed to an auditory or olfactory stimulus. If a change in the direction of attention can thus selectively inhibit afferent inflow, and if, as has been suggested, the evocation of epileptic discharge may sometimes depend upon a particular stimulus pattern, the effect of a deliberate switch of attention in arresting certain seizures might thus be explained.

Biochemistry

The biochemical factors in epilepsy must be of primary importance. The abnormalities of electric potential associated with seizures are as much an effect of ionic flux across the cell membrane as is convulsive movement, and neither can give us any direct knowledge of the essential nature of the discharging lesion. It is natural that the identification of excitatory and inhibitory

transmitter substances within the central nervous system should have been the centre of attention. So far the only one that is known is acetylcholine, which acts at the synapse of the axon collateral of the motoneurone with the Renshaw cell, and the question whether acetylcholine operates as a transmitter in the brain has been actively pursued. There is experimental evidence suggesting that acetylcholine plays a part in some epileptic seizures (Feldberg, 1956).

Another interesting line of enquiry began with the discovery by Florey (1954) that an extract of mammalian brain or spinal cord had an inhibitory effect upon the stretch receptor of the crayfish. This organ when subjected to moderate continuous stretch sends impulses up the afferent nerve at a frequency varying with the strength of the exciting stimulus. When the preparation is immersed in a solution containing small amounts of Florey's inhibitory, or I, factor these impulses cease and return as soon as the solution has been washed off. The I factor has since been identified as γ-amino-butyric acid (GABA) (Bazemore *et al.*, 1957). The effects of topical application of GABA to the cortex have now been studied in some detail (Purpura *et al.*, 1957; Iwama and Jasper, 1957), and it is agreed that it abolishes the surface negative response to direct cortical stimulation with the appearance in its stead of a surface positive wave. Its effect upon potentials evoked in the cortex by stimulation of the sensory nucleus of the thalamus is to abolish the surface negative element of the normal diphasic response with an apparent small increase in the surface positive component. Whether the surface negative component has its origin in the apical dendrites, or in independent superficial neurones, is uncertain, but in either case it is assumed to be the effect of synaptic excitation. GABA therefore appears to block excitation in the superficial layer of the cortex, and unmask inhibition, and its action thus resembles, but is opposite to, that of strychnine. It is therefore not surprising that it has been found that oral premedication with GABA will protect animals against convulsions artificially induced by chemical means (Hawkins and Sarett, 1957).

GABA is present in considerable quantity in the brain, being formed *in situ* from glutamic acid by the catalytic effect of an enzyme which requires as co-enzyme pyridoxal phosphate. This is of interest as it has long been known that one of the symptoms resulting from pyridoxine deficiency in animals is epilepsy. Of further interest have been clinical observations reported from the U.S.A. The first of these concerned the case of an infant in whom constant and intractable convulsions began three hours after birth (Hunt *et al.*, 1954). The child was admitted to hospital at the age of 2 weeks and the history contained the observation that there had been two brief periods of freedom following an injection of a proprietary vitamin compound. This was confirmed, and by analysis and the process of elimination it was proved that the anti-convulsant factor in the compound was pyridoxine. It was then found that a daily dose of 2 mg. of pyridoxine orally controlled the seizures absolutely so that there was no recurrence except when the dose was omitted. In this case, therefore, there appears to have been an inborn error of metabolism, possibly familial, as a sibling had begun to have convulsions four hours after birth and died at the age of 30 hours. Comparable cases have since been reported (Bessey *et al.*, 1957). Another observation was that of a widespread epidemic throughout the U.S.A. of generalized seizures in infants, beginning between the ages of 2 to 4 months and usually occurring several times a day. It eventually transpired that all these infants had been artificially fed and that the food they had been given was a particular brand of liquid milk substitute. When they were fed with another brand of milk substitute the seizures ceased. Analysis of the responsible milk substitute showed a gross deficiency of pyridoxine content as compared with similar preparations, this being due to a new method of sterilization which involved excessive heating. The preparation was withdrawn from the market and the epidemic ceased (Moloney and Parmelee, 1954; Coursin, 1954, 1956).

These observations suggest that GABA may be a natural anti-convulsant, present and formed in the brain, and that, when its production from glutamic acid is obstructed by pyridoxine deficiency, epilepsy is one of the results, at any rate in infants. From the evidence at present available it would appear that GABA is not an inhibitory transmitter substance, but that it blocks excitation, and that this effect is not confined to the sub-synaptic inhibitory areas but extends to the whole soma-dendritic membrane (Kuffler and Edwards, 1958). Elliott (1958) suggests that GABA exists in the interstitial fluids and exerts continuous effects on neuronal activity.

Reverting to the stretch receptor organ of the crayfish, we find another observation that may be relevant to an old-standing problem. Elliott and Florey (1956) have found that picrotoxin and Metrazol do not obviously affect the activity of the stretch receptor neurone, but that both substances prevent the inhibitory effect on the preparation of relatively high concentrations of factor I or GABA. Strychnine does not show this effect. Picrotoxin and Metrazol in high

dosage are convulsants in the crayfish, while strychnine is not. In fact the potencies of picrotoxin and Metrazol as convulsants in the crayfish are roughly inversely proportional to the concentrations of these drugs required to prevent the action of factor I. It has further been observed in mice that seizures induced by Metrazol can be prevented by oral premedication with GABA (Hawkins and Sarett, 1957). We may here have a clue to the convulsant action of Metrazol in man for which there has never been any satisfactory explanation.

Other recent observations that may be relevant to epilepsy are those upon the nature and functions of the blood-brain barrier (Bakay, 1956). Most substances when injected into a vein or into the peritoneum in animals penetrate the brain slowly and are thus found later and in smaller quantity than in other organs. Moreover, having gained entry to the brain, they are equally slow to pass the barrier in the other direction. The blood-brain barrier, as Tower (1958) has remarked, "functions as a homeostatic mechanism to stabilize the neuronal environment and confers upon the central nervous system a considerable degree of biochemical autonomy". The recent work of Millen and Hess (1958) has suggested that the barrier lies in the ground substance between the capillaries and the neuroglial feltwork and that the ground substance is a muco-polysaccharide. Local injury to the surface of the brain, as by a hot needle, ruptures the capillaries and injures the perivascular ground substance, thus allowing vital dyes and other substances to gain access to the intercellular spaces of the brain. Penetration of these substances beyond the area of injury is prevented by the undamaged ground substance in the surrounding uninjured areas. These observations introduce the possibility of a local accumulation in excess of substances having an excitatory or inhibitory effect as the result of an inward leakage from plasma to brain. The opposite possibility must also be allowed for—leakage from brain to plasma.

Recent experiments by Purpura *et al.* (1958) are of interest in this connexion. They first observed that the intravenous injection of γ-amino-butyric acid produces neither any alteration of surface potentials nor any detectable increase in the brain concentration of GABA, thus confirming other evidence showing that GABA does not effectively penetrate the blood-brain barrier. They then proceeded to effect local damage to the cortex and found that under these conditions GABA given systemically caused changes of electrical potential confined to the region of the local barrier breakdown, comparable with those produced by topical application. Of further interest was the observation confirming previous work, that in the neighbourhood of a lesion produced by freezing with ethyl chloride spontaneous paroxysmal activity would develop—in fact a spike focus. Under these conditions the injection intravenously of GABA caused disappearance of the negative spike, the appearance of high-voltage positive sharp waves, and at the end of about 12 seconds a normal record. The injection of GABA in large amounts, 30 mg./kg., would abolish paroxysmal activity for several hours. The authors note that the inhibitory effect thus produced is greater and much more prolonged than that following the topical application of GABA in the region of a spike focus.

Clinical Problems

From this brief review it would appear that there is physiological and biochemical support for the existence of inhibitory systems in the brain which have among their functions that of an anticonvulsant, and that a failure in one or other of these systems may suffice to cause epileptic seizures. This hypothesis does not exclude the possibility of primary excitation, such as might result from an excess of excitatory transmitter substance, having the same effect. There is indeed experimental evidence which supports this.

I shall conclude by presenting some facts of clinical observation which in the absence of scientific interpretation invite speculation. The first is the occurrence of seizures resulting from the presence of an extracerebral tumour, for example a meningioma lying upon the motor cortex. To begin with some assumptions, let us suppose that the persistent discharging lesion, in Jackson's sense, is caused by a local disorder of function involving a block of inhibition or enhancement of excitation. This is generally supposed to be the effect of local circulatory disorder. The next assumption often made is that the seizures are an effect of anoxia. This, however, receives little support from experiment or clinical enquiry. The local ischæmic episodes which we commonly observe as the result of arterial narrowing usually take the form not of an epileptic seizure but transient loss of function. Another possibility would be the local accumulation of waste products as the result of venous obstruction. This has been investigated, so far with negative results (Pope *et al.*, 1946). A further possibility worth consideration is whether, either as the result of vascular congestion or deformation of the brain, there may be a local breach in the blood-brain barrier, with local accumulation of a substance which enhances excitation or blocks inhibition; or on the other

hand leakage from the brain of an inhibitory substance. This, however, is mere speculation, and it has to be admitted that the question of how a meningioma causes seizures is unsolved. Even if it were answered there remain others. Why are the seizures only occasional and by what are they occasioned? This is, of course, a question that applies to epileptic seizures in general, and to which the answer may be in part that seizures may be evoked by specific stimulus patterns. If, as has already been suggested, there is under normal conditions a variable and fluctuating control of afferent inflow, the coincidence in time of two factors, specific stimulus and weak inhibition, might be necessary. It seems essential, however, to invoke another factor of a more general kind, if only to explain why of two patients having apparently identical tumours one has frequent seizures and the other few or none. Into this field of enquiry I shall not venture.

We sometimes observe cases in which after a "spontaneous" seizure the patient is confident, with good reason, that he will have a period of complete freedom, and a refractory period may also occasionally be observed after evoked seizures. Through the kindness of Mr. Falconer I have had the opportunity of examining a patient under his care in whom the refractory state was of exceptional interest (Falconer and James, 1959). The case is to be published, but I have permission to refer in advance to those observations which are relevant to the problems under consideration.

The patient, a very intelligent male aged 18, was subject to spontaneous seizures, which at the time of his admission to hospital would occur three or four times daily. The attacks were brief and not necessarily attended by loss of consciousness but often caused him to fall, and were therefore a cause not only of inconvenience but danger. He had been aware for some time that after a seizure he would be immune for several hours. He had also learned that he could elicit an attack by rubbing the right side of his face with the back of his right hand. This rubbing, if repeated at a certain rate, would, if the attempt were successful, evoke a sensation described as like something caressing the right cheek and temple. This sensation would then continue spontaneously in a rhythmic or pulsating fashion and end in a seizure. He could usually thus precipitate a seizure if he had had no attack in the preceding two hours, but the shorter the time he had been without a seizure the greater was the duration of the rubbing required to provoke one. Observation by Dr. James revealed a remarkably constant inverse relationship between the amount of stimulation required and the length of time since the last attack. The patient, who was leading an active life, had made practical use of his knowledge, and would retire to a convenient place and provoke a seizure in order to prevent such an occurrence in awkward situations. He proved at operation to have an angiomatous malformation at an appropriate site in the left post-central gyrus.

There appear to be at least two possible modes of interpreting these observations. According to the first, the local accumulation of an excitatory substance led eventually to an excessive discharge. The excitatory substance, being presumed to be a precursor of the excitatory transmitter substance, was exhausted in the course of the discharge and the refractory period corresponded with that required for re-accumulation. The hypothetical excitatory substance might conceivably be a constituent of normal plasma accumulating locally in excess owing to a leak in the blood-brain barrier. An alternative hypothesis would be that the effect of the local lesion was depression of the tonic inhibitory control of afferent impulses. Either chance stimulation of the appropriate area, or self-stimulation, initiated a seizure. The excitation then evoked local augmentation of inhibition, which, having caused cessation of the discharge, continued as a tonic inhibitory state with a gradual decay up to the point at which first a large, and then a smaller, volley of afferent impulses would break through, and finally, if no attack were artificially evoked, the normal afferent inflow would provoke an apparently spontaneous attack. If this latter interpretation should be correct we still have to enquire what are the chemical processes underlying this sequence of events, but it would at least be possible to imagine the local lesion to be causing a defect of function, that is to say, a defect of inhibitory function, which would bring it into line with what has been suggested in myoclonic seizures, and is generally a more satisfactory kind of explanation for the clinician and pathologist than that implied by the concept of local irritation.

Conclusion

It has been possible in this lecture to discuss only a few of the recent advances in neurophysiology and biochemistry. It is in the latter field that further discoveries are to be hoped for which will throw a light into the many dark corners which are now open only to speculation. When the transmitter substances in the brain are known, together with their backgrounds of enzyme and substrate, and when the chemical environment of the nerve cell and its susceptibility to changes in the constituents of the plasma are better understood, the neurologist may feel less bewildered by the problem of epilepsy than he is to-day. Meanwhile the work of Hughlings Jackson stands as an example for all students of epilepsy not only to record their

observations in the greatest detail but to be constantly asking questions about all that has been observed.

I am greatly indebted to Dr. C. G. Phillips and Professor R. H. S. Thompson for their advice and encouragement in the preparation of this lecture.

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DISCUSSION: TRACHEOSTOMY TO-DAY

Mr. Terence Cawthorne, Mr. A. B. Hewlett and **Mr. Douglas Ranger** (London):

Tracheostomy in a Respiratory Unit at a Neurological Hospital

Introduction

Before plunging into the present state of tracheostomy, it will, we hope, be of interest to glance back for a few moments into the way in which this life-saving and dramatic operation has developed.

Opening into the trachea for the relief of laryngeal obstruction was first mentioned by Asclepiades, a Greek physician practising in Rome in the first century B.C.

Paul of Aegina in the seventh century A.D., and Rhazes the Arabian physician in the ninth century A.D., each gave indications for and described the operation of tracheostomy.

Then in the Middle Ages from the famous medical school of Padua came the following description of the operation by Fabricius who occupied the Chair of Anatomy and Surgery at the turn of the sixteenth century:

"Of all the surgical operations which are performed in man for the preservation of his life by the physician, I have always judged to be the foremost that by which man is recalled from a quick death to a sudden repossession of life. The operation is the opening of the aspera arteria by which patients, from a condition of almost suffocating obstruction to respiration, suddenly regain consciousness, and draw again into their heart and lungs that vital æther, the air, so necessary to life, and again resume an existence which had been all but annihilated."

His pupil and successor, Julius Casserius (1552–1616), illustrated the operation and the instruments then in use in his treatise on anatomy, medicine and surgery.

Thomas Fienus, Professor of Medicine at the University of Louvain, first used the word tracheotomy in 1649, and the Frenchman, Pierre Bretonneau of Tours, at the time of Napoleon Bonaparte, advocated it for diphtheria, which owes its name to him.

It remained for our teacher and colleague, Negus (1938), to suggest the term "tracheostomy" for a maintained opening in the trachea.

There are many examples both in history and in fiction of dramatic episodes in which lives were saved by a timely opening of the windpipe, but those of us who have had to face the horrors of an emergency tracheostomy without proper equipment and sometimes *coram populo* prefer to forget the experience.

Until 1930 tracheostomy was reserved for cases of respiratory obstruction at or above the level of the larynx, but Wilson (1932) and Davidson (1936) suggested tracheostomy for the relief of respiratory insufficiency due to the bulbar form of poliomyelitis. About this time too the operation was suggested as an alternative to repeated bronchoscopy for the removal of secretions in acute laryngo-tracheo-bronchitis in children. Galloway (1943) has been a strong advocate of tracheostomy for respiratory emergencies from whatever cause and the poliomyelitis epidemic in Denmark in 1952 finally convinced the medical world that tracheostomy could be a life-saving measure in respiratory insufficiency arising from any part of the respiratory tract.

Tracheostomy To-day

A not unnatural reluctance to embark upon an operation which, it was thought, might in itself be serious and even mutilating has gradually disappeared now that it is realized how effective, time-saving, and life-saving it can be. Moreover it is free from unpleasant sequelæ, provided that the entrance into the trachea is made below the first cartilaginous ring.

The tendency for more and more operations to be done for respiratory emergencies other than the traditional one of laryngeal obstruction is well illustrated in Table I, made up from figures quoted by Nelson (1958).

TABLE I.—TRACHEOSTOMY (NELSON, 1958)

	For laryngeal obstruction	For other causes of respiratory insufficiency
1940	98%	2%
1954	53%	47%
1958	48%	52%

Thus within the past 20 years the indications for tracheostomy have extended beyond the classical and obvious one of relieving obstruction to the entry of air into the tracheobronchial tree, and now more than half the operations are performed to prevent or to overcome respiratory insufficiency from other causes.

The present-day indications for tracheostomy are set out in Table II and they are placed in order of their development.

TABLE II.—INDICATIONS FOR TRACHEOSTOMY

1.	To relieve obstructive laryngeal dyspnœa.
2.	To facilitate removal of secretions retained within the tracheobronchial tree.
3.	To discourage anything but air from entering the tracheobronchial tree.
4.	To assist respiration by reduction of the dead space.
5.	To isolate the respiratory tract from the digestive tract.
6.	To permit positive pressure respiration.

Now, the importance of removing secretions from the lower respiratory tract was first stressed by Chevalier Jackson (1911), who coined the phrase "patients drowning in their own secretions". By means of bronchoscopy, and using mechanical suction, he was able to save many lives, but the disadvantage of this method was that a bronchoscope had to be passed each time aspiration was needed.

Then the increasing use of intratracheal anæsthesia following the introduction by Magill (1928) of the soft wide-bore tube passed through the nose or mouth and through the larynx into the trachea, and the more general use of mechanical suction in operating theatres, encouraged anæsthetists to aspirate secretions from the lower respiratory tract. At first this was done via the wide-bore intratracheal tube, but with the developments in thoracic surgery, fine rubber catheters through the larynx and down to the bronchi were used.

As the iron lung or tank respirators came into use for the maintenance of respiration in cases in which the respiratory muscles were paralysed by poliomyelitis, it was found that where the pharyngeal muscles were also paralysed, saliva and food could often not be prevented from entering the tracheobronchial tree through the paralysed larynx.

Galloway, the Chicago laryngologist, led the way in pointing out the value of tracheostomy in discouraging the sucking in of pharyngeal secretions through the paralysed and open larynx with each forced and artificial inspiration.

The extended use of intratracheal anæsthesia and in particular the use of closed circuit machines made the anæsthetists appreciate the potential danger of dead space air, particularly when the breathing was shallow. From this has come the realization that, in the shallow respiration of profound unconsciousness, the reduction of the dead space air from 150 c.c. to 50 c.c. by means of tracheostomy may in itself be life saving.

Finally the introduction by anæsthetists of the cuffed intratracheal tube, which effectively isolates the lower respiratory tract from the digestive tract and at the same time allows for positive pressure respiration, has solved the problem of "inhalation pneumonia", and has almost rendered the iron lung obsolete; and there can be few, if any, of those who have had to cope with patients in iron lungs who will regret this.

The stimulus for this last step came from Denmark when in 1952 they were struck by a serious epidemic of poliomyelitis with many cases of respiratory paralysis and not enough iron lungs to go round. They had to improvise, and by means of tracheostomy with cuffed tubes and by using teams of medical students to operate manually the positive pressure apparatus, many lives were saved. This led to the development of the mechanical positive pressure breathing machine. In this country there are two such machines in general use, one developed by our colleague Dr. Beaver, the Senior Anæsthetist at the National Hospital for Nervous Diseases, Queen Square, in the Respiratory Unit, and the other by the Respiratory Unit at the Radcliffe Infirmary, Oxford (Beaver, 1953; Russell and Schuster, 1953).

The anæsthetist has come to play an increasingly important part in the management of respiratory emergencies, particularly in their early stages. Often an intratracheal tube passed through the larynx and connected to a positive pressure machine will tide a patient over until it can be decided when and where a tracheostomy should be done.

We have seen several patients who had such a tube in place for up to eighteen hours without any subsequent harm, but when there are active laryngeal movements it would not be wise to leave the tube so long as this. Another reason we have for being grateful to our anæsthetic colleagues is that instead of having to face the horror and anxiety of a hurried emergency tracheostomy in a bedroom, it is now possible to do it deliberately and calmly in appropriate surroundings, often on an anæsthetized and intubated patient.

So far we have considered the indications for tracheostomy, and there is no need to go into the details of the operation except to stress the importance of leaving the cricoid cartilage and if possible the first ring of the trachea intact in order to avoid subsequent laryngeal stenosis.

Having got the tube into the trachea, the time will come when the tube will need to be taken out and this can sometimes be a problem, particularly if there has been pharyngeal and laryngeal paralysis. When a patient has worn a tracheostomy tube for some time, he becomes very dependent upon mechanical suction to clear secretions from his lower respiratory tract. If in addition the tube has been cuffed and the larynx at any rate partly paralysed, a pool of accumu-

lated saliva will occupy the laryngopharynx, the laryngeal entrance, and that part of the trachea above the tube. In consequence the larynx will lose its normal protective reflex of closure and coughing in response to anything but air trying to get past it, and it may take some time for the laryngeal reflex to develop again.

Another factor to be considered in decannulation is the expulsive power of the cough. As paralysis of the respiratory muscles wears off, coughing returns; but it may be some time before the cough is sufficiently strong to expel all unwanted secretion from the tracheobronchial tree. Also the patient has become used to artificial aids to breathing and to mechanical suction as an alternative to coughing. He not unnaturally dreads the change over, and particularly in paralytic cases it may take time to wean him away from his tube.

A wise rule is not to remove the tube until the patient can sleep through the night with it completely corked.

Very often a patient will be quite content to have the tube corked day and night provided every few hours it can be uncorked and accumulated secretions sucked out.

Any acute respiratory tract infection will increase the amount of secretion and decannulation will have to be postponed.

Once the tube is out, the tracheostomy closes very quickly, and the resulting scar is rarely conspicuous.

a Respiratory Unit was set up at the National Hospital for Nervous Diseases, Queen Square, under the direction of Dr. Michael Kremer. Dr. Beaver developed his breathing machines and we did the tracheostomies. At first the patients were cases of poliomyelitis or polyneuritis and they were in iron lungs. This made the tracheostomy operation and its subsequent care difficult. Once the positive pressure breathing machine had been devised and we had a suitable rubber tracheostomy tube with inflatable cuff, the

Our experience of tracheostomy for lower respiratory tract emergencies dates from 1953 when patients were all dealt with in this way, and except for an occasional patient being admitted who had been in an iron lung for some days or even longer, we have not needed to use the iron lung for some four years.

Another smaller group which has needed tracheostomy is of cases of myasthenia gravis. These cases do not do well despite the relief given to respiration.

Finally there are the cases of profound unconsciousness due to some intracranial damage, infection, vascular accident, or to poisoning. In these cases tracheostomy alone without assisted respiration often suffices.

There are still, of course, the cases of laryngeal obstruction which need tracheostomy, but more often than not the surgeon is able to work leisurely, comfortably, and safely, thanks to an indwelling intratracheal tube.

We have not in this short review attempted to cover the whole field, but have mentioned those cases of which we have had personal experience.

In conclusion, we think that it can safely be said tracheostomy need never harm a patient but it can save many lives.

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Mr. Austin E. Wheatley (London):

Some Aspects of the Use of Tracheostomy in General Surgery

I propose to discuss here the principles underlying the use of tracheostomy in general surgery. The indications for tracheostomy are as follows:

(1) *Respiratory obstruction.*

(2) *Respiratory paralysis.*

(3) *Respiratory disease.*—It is this group, which especially affects the general surgeon, that I intend to discuss. In respiratory disease the indications for tracheostomy fall into 3 groups.

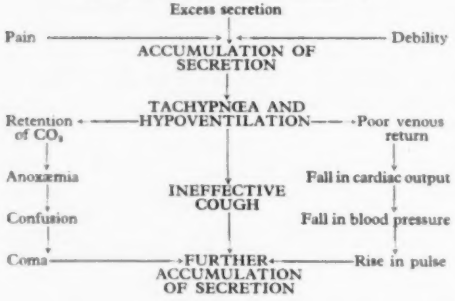
(*a*) *Coma* has been discussed by Mr. Terence Cawthorne and will be dealt with also by Mr. Walpole Lewin.

(*b*) *Following operations on the neck and jaws:* Tracheostomy is often life-saving in these cases. Blood and serum may collect in the pharynx post-operatively. Together with swelling of the tongue and immobility of the jaws there may be difficulty in respiration and expectoration, and a

risk of aspiration pneumonia. Tracheostomy, which we have never regretted performing, is usually required only for a few days.

(*c*) *The "wet lung" syndrome* (*see* Table I):

TABLE I.—THE WET LUNG SYNDROME



Here I have grouped together all the cases in which the tracheobronchial system becomes flooded with secretion. This may be due to a variety of causes, including the following: inability to cough effectively because of pain from fractured ribs or an operation wound; overproduction of secretion as in acute bronchitis or lung contusion; or in general debility, as after a major operation in the elderly.

With accumulation of secretion the respiratory rate increases, respiration becomes more shallow, coughing is less effective; there is further accumulation of secretion and a vicious circle is set up. The efficiency of the venous thoracic pump is reduced, the cardiac output and blood pressure fall, the general condition deteriorates, and the pulse rises. Biochemically, CO_2 is retained, anoxæmia occurs, the level of consciousness is depressed, and the patient cannot co-operate. The result is a restless, semi-conscious, blue patient, with ineffective shallow respirations and a bubbling chest, in early peripheral circulatory failure.

The causes of this syndrome that we have met are as follows:

(1) *Trauma*
- (*a*) Multiple fractures of the thoracic cage.
- (*b*) Paradoxical respiration from fractures or thoracoplasty.
- (*c*) Lung contusion: or a combination of all three.

(2) *Post-operative*
- (*a*) Failure to cough, in debilitated patients.
- (*b*) "Post-operative bronchitis."
- (*c*) Thoracic surgery in patients with a poor respiratory reserve.

(3) *Acute pulmonary infection*

These cases have been mainly due to an exacerbation of bronchitis with anoxæmia, narcosis and cardiac failure.

Treatment.—Minor forms of this condition are very common. With the aid of physiotherapy and good nursing, provided the patient can cough and get rid of secretion, no further treatment is necessary. Prophylaxis, in the form of preoperative treatment, and tracheobronchial toilet at the end of an operation are of greatest importance. Often, however, the type of patient who develops this syndrome has had an emergency operation or is the victim of accidental trauma.

Bronchoscopy may be of great value in clearing secretion away, and with the resulting improvement the patient can cope with the situation himself. Sometimes secretion accumulates so quickly, especially under the circumstances I have mentioned, that further bronchoscopy is required in a few hours. Apart from the distress that this causes the patient, repeated bronchoscopy is not without its dangers. A tracheostomy, on the other hand, is not distressing and allows repeated easy removal of secretion. For the patient who is already in great distress, I would recommend immediate tracheostomy. In others I have performed a bronchoscopy first, but if this needs repeating within a short time, then I do not hesitate to make an opening in the trachea.

The benefits which accrue from tracheostomy are as follows:

(1) *Stoma for aspiration of secretion.*

(2) *Reduction in the dead space.*—Of the total tidal air, one-third is normally dead space, and plays no part in respiration. When the tidal air is reduced, the dead space may become as much as one-half of the total tidal air. When tracheostomy is performed, the dead space is greatly reduced, so that it only occupies about one-seventh of the total tidal air, and so the patient can get more air into his chest with less effort than previously.

(3) *Decreased resistance to respiration.*—By removing the resistance at the glottis, the muscular work required for respiration is lessened.

(4) *Decreased respiratory rate*, leading to an improvement in venous return, cardiac output, and blood pressure.

(5) *The oxygen requirement is reduced*, as seen by the reduction in dead space and lessening of muscular activity.

(6) *Loss of retained CO_2.*—With improvement of respiration and removal of secretion, excess CO_2 is washed out of the circulation.

Conclusion.—The nursing of a patient with a "wet lung" syndrome is made considerably easier

by the performance of a tracheostomy, ensuring a rested co-operative patient.

In our series, no death has been directly attributed to the tracheostomy. The tracheostomy has been required for up to seven days, and we have experienced no difficulty in decannulation. Although we have never regretted performing a tracheostomy, many times we have regretted not performing one at an earlier stage. As our experience has grown, so we have had to use this as a method of treatment and prophylaxis more and more.

I wish to acknowledge the help of the Ear, Nose and Throat Department of King's College Hospital, especially Mr. Terence Cawthorne, Mr. R. S. Lewis and Mr. B. H. Pickard, and also the great help and stimulation that I have received from Dr. S. A. Mason, Mr. W. P. Cleland, and Mr. A. J. Heriot.

Dr. Beryl D. Corner (Bristol):

Tracheostomy in Pædiatrics

Tracheostomy is used by the pædiatrician for two main reasons: (1) The relief of severe upper respiratory obstruction. (2) For removal of secretions, crusts or membrane from the trachea and main bronchi when cough or aspiration through an intratracheal tube or bronchoscope is ineffective.

Indications in Infancy

Improved early diagnosis and care of young infants has now rendered radical surgery possible, so that tracheostomy in the newborn is often planned as the first stage of a long treatment programme for congenital malformations of the upper respiratory tract. Bigler *et al.* (1954) reported that of 62 tracheostomies in infancy 33 were performed for congenital lesions, usually in the first four months, as compared with 18 for inflammation, the incidence of the latter showing a decline during the seventeen-year period under review. Laryngeal obstruction caused by papillomata or fibromata also presents most frequently in the first eighteen months (Kohlmoos, 1955). In recent years in Bristol, tracheostomy has been performed in 4 newborn infants for congenital malformation, and once successfully for hæmolytic streptococcal laryngeal œdema.

Older Children

After the first year, acute laryngo-tracheobronchitis ("croup") is the most important condition requiring tracheostomy. Obstruction by foreign bodies, laryngeal œdema and tumours is by comparison very rare.

This is now one of the most serious infective disorders of the first seven years with a high mortality rate compared with the exanthemata (Emery, 1952). The incidence of severe cases necessitating tracheostomy is highest in the second to fourth years (Turner, 1954). Usual organisms isolated are *Staphylococcus aureus*, *Hæmophilus influenzæ* or hæmolytic streptococci, although viruses are probably responsible for many cases.

Initial coryza and hoarse cough progress rapidly to stridor and respiratory obstruction, which occur very readily in childhood due to the small aperture of the glottis and the highly vascular, loose submucosal connective tissue which permits rapid development of œdema and spread of infection. Sometimes obstruction is entirely in the trachea due to mucosal œdema and characteristically viscid secretion, crusts or membrane which are also liable to obstruct the larger bronchi.

Immediate tracheostomy is indicated if most of the following signs are present:

(1) Restlessness despite adequate sedation. This is the most important prognostic sign.

(2) Cyanosis or greyish pallor.

(3) Pulse-rate persistently 160/minute or above.

(4) Increasing respiration rate and stridor.

(5) Severe and increasing indrawing of the costal, supra- and sub-sternal soft tissues.

(6) Diminished pulmonary air entry.

(7) Fatigue.

At an earlier stage constant skilled nursing supervision is essential, and preparations for tracheostomy must be made. The following plan of medical treatment is started:

(1) Barbiturate sedation; opium derivatives and atropine are dangerous.

(2) Steam tent or oxygen with detergent mist. An oxygen concentration above 50% is undesirable owing to the drying effect on the respiratory secretions.

(3) A broad-spectrum antibiotic.

Deterioration despite adequate treatment is the indication for urgent tracheostomy.

The value of pre-operative laryngoscopy is limited as tracheal obstruction cannot be excluded and dangerous laryngeal spasm may occur. Pre-operative bronchoscopy or intubation to maintain the airway and to allow for suction or anæsthesia is valuable (Fearon, 1954). The widest bore tracheostomy tube should always be used.

Post-operative care.—The aims are: (1) Suppression of bacterial toxæmia and prevention of secondary infection by correct antibiotic treatment. (2) Maintenance of the airway, which is often very difficult owing to the gelatinous nature

of the exudate and the tendency to bronchial obstruction. These measures are important:

(*a*) Adequate hydration.

(*b*) Inhalation of detergent mists or steam.

(*c*) Frequent aspiration with a moistened catheter, aided by prior instillation of a few drops of saline or streptomycin–streptokinase solution into the trachea.

(*d*) Frequent auscultation of the lungs and intensive percussion therapy if bronchial obstruction threatens.

The outer tube can usually be removed in three to five days and the wound rapidly heals.

In this disease mortality is not due to operation, which is a life-saving measure, but to delay in its performance. Modern treatment has reduced deaths from rates as high as 35% of operated cases (Morgan and Wishart, 1947) to single figures in the last decade (Turner, 1954).

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Dr. A. Crampton-Smith (Oxford):

Tracheostomy and the Anæsthetist

Since 1953 I have been associated with Dr. J. M. K. Spalding in the treatment of patients with respiratory weakness, often complicated by dysphagia, by artificial ventilation through a cuffed rubber tracheotomy tube. This tube serves the dual purpose of separating pharynx from trachea and of providing a convenient route for a pump to apply artificial ventilation.

The patients whom we treat suffer from poliomyelitis, polyneuritis, barbiturate poisoning, tetanus, myasthenia gravis, and post-operative respiratory insufficiency.

The complicated routine of treatment of these patients could not be described in the time at my disposal, so I shall discuss only the prevention and treatment of chest infections in artificially ventilated patients, and the assessment of their ventilation.

Patients who require artificial ventilation are prevented by their paralysis from coughing, and this in association with the introduction of infection by suction catheters, and the additional secretions produced by the presence of a tracheotomy tube, makes our patients particularly liable to chest infections which may be life threatening.

In Oxford we rely on three measures to prevent chest infection. They are:

(1) *Change of posture and physiotherapy to the chest.*—Skilled nursing and physiotherapy are of great importance in the treatment of these patients.

Our patients are turned from lateral to lateral position two-hourly, and have "rib springing" in the appropriate position for drainage of each lobe of each lung by a physiotherapist up to four times daily.

(2) *Tracheobronchial toilet.*—Our nurses routinely use a sterile whistle-tipped rubber catheter for suction through the tracheotomy tube. These almost always find their way into the right side, but it is usually possible to manœuvre an angled catheter into the left side.

(3) *Humidification of inspired gases.*—We compensate for the loss of the normal humidifying apparatus by passing the inspired gases over hot water to our patients, so that the inspired gases reach the patient saturated with water vapour at about body temperature.

If in spite of these measures part of the lung does become infected, they are intensified, and the patient spends more time in the position most likely to drain the affected area. Antibiotics are used as indicated, but bronchoscopy is not.

The assessment of ventilation in these patients is by no means as straightforward as it at first appears. The reversal of the normal intrathoracic pressure changes during artificial ventilation and the conflicting requirements of the lungs and the circulation make it desirable to assess the ventilation as accurately as possible.

At Oxford we still rely mainly on the measurement of expired air as a means of assessing ventilation in clinical practice. We try to keep our patients' measured expired air close to the respiratory minute volume calculated to be adequate for their requirements.

Blood gas analysis is also used as an index of the adequacy of ventilation. Its disadvantages are that it requires an arterial puncture, can only reflect conditions existing at a moment of time, and that the analysis involves the employment of fairly complicated techniques. In certain circumstances, however, notably in patients with emphysema or other pulmonary disease, it may be the only way of acquiring the information necessary to judge whether ventilation is adequate.

The pCO_2 of end tidal air is close to that of arterial blood in normal subjects, and end tidal air can be relatively easily collected and analysed and its pCO_2 used as an index of ventilation. Unfortunately, when the lungs are abnormal, there may be a considerable difference between

the pCO_2 of end tidal air and arterial blood. Rebreathing techniques directed to equilibrating the pCO_2 of gas mixtures in a bag with that of mixed venous blood may circumvent this difficulty.

In respect of oxygen, ear oximetry is unreliable in patients in whom periphero-vascular stasis exists.

The complexity of the assessment of ventilation has been stressed only to emphasize the fact that many lives may be saved by artificial ventilation when only clinical judgment and simple measurements are available to those responsible for treatment.

Mr. Walpole Lewin (Oxford):

Tracheostomy in Head Injuries

Difficulties in maintaining the airway in the unconscious patient after head injury are common, and other chest complications also frequently arise. Apart from the local complication, the cerebral effects of the resultant hypoxia added to the existing brain lesion can be disastrous. Tracheostomy has been employed in selected cases of head injury and other neurosurgical conditions for many years but as a definitive policy in the management of head injuries it has only come to the fore since the War. Several favourable reports have now appeared (Echols *et al.*, 1950; Dunsmore *et al.*, 1953; Lewin, 1953; Andrew, 1956; Maciver *et al.*, 1958).

Tracheostomy is no substitute for good nursing and it should be emphasized that in the majority of patients the airway can be maintained safely for indefinite periods with ordinary nursing measures. Endotracheal intubation and tracheostomy are required only in those patients where these simpler measures have failed or they are clearly inapplicable. In the early hours after some severe injuries where it would appear that a fatal injury has been sustained an endotracheal tube can maintain the airway until the prognosis is clearer. In most such instances the decision as to whether retention of the tube is all that is needed or whether it should be replaced by a tracheostomy can usually be made within eight hours, or twelve hours at the most. A second useful indication for endotracheal intubation is as a temporary measure where unconscious patients are being transferred to a neurosurgical centre for further treatment and difficulty with the airway is envisaged during the journey. We do not favour, however, their routine use in head injury cases for in our experience retention of these tubes for more than a few hours has led inevitably to suppurative tracheitis.

The observations in this paper are based on experience in the Accident Service of the Radcliffe Infirmary, Oxford. In the ten years from November 1948 to October 1958, 5,000 consecutive cases of head injury were admitted with an overall mortality of 5·3%. In that time and beginning in March 1949, 100 tracheostomies were performed.[1]

Indications for Tracheostomy

Over the last ten years we have come to divide the patients in whom this operation has to be considered into the following groups:

(1) *Severe head injury alone.*—These patients are admitted comatose with flaccid limbs, or, either at once or within a few hours, show a considerable increase in extensor tone which may go on to decerebration and decerebrate attacks with hyperpyrexia and a rapid pulse and respiration. In many of these patients where tracheostomy has to be considered, the pupils are irregular and react sluggishly or are fixed to light, but in some they may be equal and reacting normally. This situation, although at all times grave, is by no means hopeless and many of these patients can survive and recover to return to their homes and work. To achieve this requires treatment from many points of view, but one necessity is a completely free airway at all times. Where it appears, therefore, that the patient is going to survive the immediate effects of the injury and in whom there is any difficulty with the airway, shown by the fact that the chest requires frequent suction, or the secretions are viscid and difficult to remove, or signs of fluid in the lung develop on examination, or if the respiratory exchange is inadequate, then an early elective tracheostomy should be considered. One should not wait until the patient is *in extremis*, or until a fully developed lung infection is evident.

It has been suggested that tracheostomy should become a routine procedure shortly after admission in all such cases. This would not appear to be necessary if only for the one reason that many of these patients can be nursed safely and effectively without it. For example, in the last 1,000 cases in which 28 tracheostomies were performed, there were 27 other patients with a similar comatose state on admission but who were not thought to need tracheostomy and who went on to make good recoveries. When to this fact is added the very definite although usually small incidence of complications after tracheostomy, one would be reluctant to make this operation a routine and would prefer to select each case on its merits. Nevertheless, it is true that where there is any doubt it is safer to go

[1]Five other tracheostomies performed in this series have been excluded as they were not related to the head injury problem (cervical cord injury with quadriplegia in 3, and miscellaneous causes in 2).

ahead with the operation. The best functional results occur in patients where the pupils are still reacting to light on admission or where there is in the history a period after the injury, however brief, in which the patient's conscious level was lighter than on admission to hospital.

Some observations on the effect of age in this group of severe head injury may be mentioned here. We are tending to be more conservative in advising tracheostomy in young children under 5 years and in patients over 65 years. Young children seem to stand the immediate effects of severe brain injury better than adults and we have had several children who have had a prolonged illness with respiratory incidents who have finally made a good recovery. This is not to dissuade the operation of tracheostomy in these young people when it is indicated but certainly to advise against its routine performance. For there is a second reason. Young children have more complications from tracheostomy. The smaller size of the trachea seems to make the operation less effective, and, perhaps because of the sensitivity of the tracheal mucosa at this age, tracheitis with crusting and bronchial obstruction has been a hazard which has caused us a lot of worry. Humidifiers are only partly effective and in recent cases we have adopted the old-fashioned routine of using a steam tent in the early days after tracheostomy, which seems better. Difficulties in weaning the young child from the tracheostomy and granulomatous overgrowth of the tracheal mucosa have also been met with in this age group.

As might be expected, older people react poorly to head injuries of this severity with or without a tracheostomy. Thus of the 43 deaths in the last 1,000 head injuries admitted, 18 were in patients over 65 years. We have not been impressed with the practical recoveries of older people from head injury with tracheostomy and in some instances the operation has served only to prolong an illness distressing for relatives and without hope of recovery. In the whole series, of 13 patients over 65 years of age who have had tracheostomies, only 1 recovered and this patient had made some improvement in the early hours and required operation later for a subdural hæmatoma. In other words the prognosis is extremely poor in the older patient who is admitted comatose and particularly with fixed pupils, and a decision for tracheostomy should be carefully taken. These comments on the age factor are limited solely to the patient with a head injury and without other complications, and do not apply where a less severe head injury together with some other factor, *vide infra*, makes a tracheostomy desirable.

One would conclude therefore that in severe head injury, tracheostomy is not needed as a routine procedure merely because a patient remains unconscious. An early tracheostomy is indicated for those patients who remain in coma and in whom the respiratory exchange is inadequate or respiratory incidents are beginning to appear; and encouraging prognostic points are patients not at the extremes of life, presence of tone in the limbs, and reacting pupils.

(2) *Fractured jaw.*—A major head injury together with fractures of the facial skeleton may demand an immediate tracheostomy. Blood may pour from these injuries down into the trachea and drown the patient unless immediate access to the trachea and bronchi with sealing off of these structures from the injured sites by a cuffed tracheostomy tube is possible. Moreover where the jaws have to be splinted in an unconscious patient a tracheostomy may be the best way to maintain the airway safely afterwards.

(3) *Chest injury.*—A head injury together with a major chest injury is a particularly lethal combination. Patients with fractured ribs and surgical emphysema with, or without, a hæmo- or pneumo-thorax can be helped very considerably by tracheostomy.

(4) *Chest disease.*—In a few patients with pre-existing chest disease such as chronic bronchitis or bronchiectasis, who then sustain a major head injury, an early tracheostomy has proved extremely beneficial. This is so particularly in older people where these chest conditions are more likely to be found and where, although a major head injury has been sustained, it is not of the severity mentioned in the first group.

It may also be mentioned here that although the accent is on prophylactic tracheostomy this should not dissuade from its performance later if pulmonary collapse or bronchopneumonia should supervene, in a patient otherwise recovering.

(5) *Fractured femur.*—Difficulty may arise here, for the position and immobilization needed to maintain adequate reduction of the femur is at variance with the treatment needed for the unconscious patient. In some instances now a tracheostomy has allowed the treatment of both conditions to proceed satisfactorily.

Complications

Tracheostomy in head injuries is nowadays usually a prophylactic operation. It is therefore important to note complications particularly if they are those which can produce the very condition of hypoxia one is trying to avoid. Davis *et al.* (1953) produced a rather alarming report of an analysis of 155 tracheostomies in which there were 155 complications of all kinds amongst about one-third of the patients. On closer analysis

they concluded that the major complications, by which was meant hæmorrhage, pneumothorax, mediastinal emphysema and apnœa, occurred in about 9% of elective procedures. These authors in the light of this experience warned against emergency tracheostomy if this could possibly be avoided. In our series of 100 tracheostomies, major complications have ensued in 8 cases, an incidence of 8%; hæmorrhage in 1, pneumothorax in 4, hypertrophic granuloma of the trachea in 1 and crusting of the trachea and bronchi, with pulmonary collapse in 2.

Results

Of 100 patients with tracheostomies, 46 died in hospital and a further 17 died at other hospitals after transfer, at periods up to fifteen months after the original injury. A third of the patients survived; in 28 of them the quality of recovery allowed them to return to their homes and work, and 4 more recent patients are still improving. These figures include the earliest cases and also those patients transferred from other hospitals, sometimes several days after injury and in whom tracheostomy was required. In the last 1,000 head injuries of the series where the indications for tracheostomy and the timing of operation have improved, of 28 patients with tracheostomy, 11 have made, or are most likely to make when convalescence is completed, a practical recovery, in other words about a third of the patients. When one considers that the operation was limited in this series to severely injured patients only, this is a worthwhile achievement since there is no doubt that nearly all of them would have lost their lives without tracheostomy. Some patients, particularly those earlier in the series, might have done better if tracheostomy had been performed sooner; and a few patients might also have benefited if a tracheostomy had been performed, but it is obvious from the overall mortality rate that these would not have been many.

Conclusions

Tracheostomy has led to the useful recovery of many patients with severe head injury who otherwise would almost certainly have died. Although it does mean that in a few others survival has been at the price of a long period of continued unconsciousness and invalidism with only a small chance of recovery, there is no certain way of knowing this in the acute stage when these decisions have to be made, although indications have been given in this communication of some factors which may be relevant. Tracheostomy, however, has to be seen as part of the armamentarium in the management of the airway of all patients after head injury. It has not only benefited some patients directly but its use has stressed the importance of the airway in the nursing of all unconscious patients.

Many developments in the management of head injuries in the post-war years have played their part in lowering the mortality, and it is at times extremely difficult to evaluate in any one patient which part of the treatment was the deciding factor. But there is no doubt of one thing: that whatever is done or not done for a head injury, an essential requirement is a free airway twenty-four hours in the day; and that in selected cases this is best achieved by an early and well planned tracheostomy.

The tracheostomies were performed by the staff of the E.N.T. Department, Radcliffe Infirmary, Oxford, and I would like to thank Mr. R. G. Macbeth and Mr. G. Livingstone for their help and co-operation at all times.

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Dr. Leslie B. Cole (Cambridge):

Tracheostomy in Tetanus

The frequency and danger of respiratory complications in tetanus have long been stressed. Trismus, dysphagia, laryngeal spasm and a fixed chest are obvious reasons and oral sepsis, excessive salivation and prolonged sedation are contributory factors. Tracheostomy helps by short-circuiting the danger points of the mouth, pharynx and larynx and provides a free airway through which bronchial secretions can be aspirated or removed by postural drainage and bronchoscopy performed on occasion. Tracheostomy may be used with sedation alone as reported by Forbes and Auld (1955) or in severe cases with relaxants and intermittent positive pressure respiration by methods similar to those of Lassen (1953) and Ibsen (1954) in the treatment of bulbar poliomyelitis. Successful results have been obtained in tetanus by both methods.

It is difficult to assess the need for tracheostomy in tetanus on reports of single cases and easier to see it in perspective against a background of a larger series. I am therefore commenting on three patients treated by tracheostomy in a series of 23 consecutive cases admitted to Addenbrooke's, Newmarket General and the West Suffolk

Hospitals during the seven-year period 1952–1958. These comprise all cases of tetanus admitted.

The classification is as follows (Table I) and the results are given in Table II.

TABLE I

Type I.	Fulminating. Incubation period (I.P.) four to ten days. Period of onset (P.O.) less than forty-eight hours. Prognosis: 99% fatal.
Type II.	Severe. I.P. seven to fourteen days. P.O. two to five days. Prognosis: 10% fatal.
Type III.	Subacute or chronic. I.P. more than fourteen days. P.O. more than six days. Convulsions mild or absent. Prognosis: 1% fatal.
Type IV.	Laryngeal. Laryngeal spasm and dysphagia predominating. Prognosis: usually good.
Type V.	Complicated. Type II and III plus lung, heart or other disease. Often in elderly. Prognosis: variable.

Local tetanus may occur in Types III, IV and V and favours a good prognosis.

TABLE II.—RESULTS OF TREATMENT OF TETANUS. 23 CONSECUTIVE PATIENTS (ALL CASES). SEVEN-YEAR PERIOD 1952–58

Type	No.	Sex		Result	
		M.	F.	Recovered	Died
I	1	1	0	0	1
II	4	2	2	4	0
III	12	7	5	12	0
IV	2	2	0	2	0
V	4	2	2	1	3
Totals	23	14	9	19 (83%)	4 (17%)

FATAL CASES
CAUSE OF DEATH

	Age	
1	7	Fulminating tetanus. Pneumonia.
2	67	Mitral incompetence and fibrillation. Pulmonary embolism nineteenth day.
3	83	Mild tetanus. Emphysema. Staphylococcal pneumonia. Moribund on admission. Died in twelve hours.
4	76	Emphysema and hypertension. Died pneumonia seventeenth day.

Comment

Type I.—The only fulminating case was in a child aged 7 admitted before intermittent positive pressure respiration was available. I.P. four days. P.O. twenty-four hours. Death in forty-eight hours. Autopsy: lungs solid with bronchopneumonia. Only tracheostomy and I.P.P.R. might have given him a chance.

Type II.—Of the 4 severe cases in this group, one adult was probably saved and management made easier by tracheostomy. 3 others in children recovered without it but might have been helped had it been done.

Type III.—All recovered without tracheostomy as would be expected.

Type IV.—Tracheostomy was performed in one of these with great benefit and might well have been done in both.

Type V.—One patient aged 76 had tracheostomy six days after admission and died of bronchopneumonia on the seventeenth day. Earlier operation might have saved her. Another aged 67, who died of pulmonary embolism on the nineteenth day after recovery from tetanus might have been saved by tracheostomy.

Summary

Tracheostomy should be done as soon as possible in all Type I cases for their only chance lies in treatment with intermittent positive pressure respiration and relaxants. In Type II it is best done early in most. Type III rarely need it but the majority of Type IV and V would probably benefit. By and large it should be used in 30 to 40% of all cases in this country. It is wiser to do it early than late.

It is important that patients should not be over-treated by too drastic sedation especially with barbiturates. It is often no advantage to control moderate or mild spasms completely. All except mild cases should be transferred as soon as possible to a centre where all facilities for investigation and treatment are available.

Finally I would emphasize that these newer methods of treating tetanus are still on trial and assessment of results depend on exact and detailed criteria—particularly of the age, sex and general physique of the patient and the presence of associated disease, the type of wound and degree of infection, the incubation period, the period of onset and the duration of the disease till death or recovery. Detailed autopsy findings are also valuable.

In conclusion I should like to express my thanks to the physicians at Addenbrooke's, the West Suffolk and Newmarket General Hospitals for their kindness in asking me to see cases under their care.

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Dr. Philip Hugh-Jones (London):

Management of Tracheostomies

The details of management of a tracheostomy will vary to some extent with the reason for its performance.

I shall not consider the design of tracheostomy tubes, nor the pros and cons of metal and plastic for their construction, although a correctly fitting tube is of prime importance. I shall consider the other practical points under the following headings: (1) The maintenance of the airway. (2) The prevention and treatment of infection. (3) The provision of adequate, but not excessive ventilation.

(1) *The Maintenance of the Airway*

Sucking out.—Regular sucking of secretions from the bronchial tree is needed in most patients who have a tracheostomy. The rubber tubing used on the sucker should be sterilized especially in hospitals to avoid cross-infection. It should be as large as possible when the secretions are very thick as after status asthmaticus or in purulent bronchitis with respiratory failure. Finally, it is important to use a catheter with a curved tip and a means of identifying the direction of the curve from the proximal end, such as a Tieman's catheter, so that the left side of the bronchial tree as well as the right can be sucked out. A straight rubber catheter usually passes down the right main bronchus only, and obstruction of the left lung by purulent secretions may readily occur in a weak or comatose patient who cannot cough.

Wetting inhaled gas.—The normal ciliary flow of mucus is interrupted by tracheostomy so that crusting from dried secretions readily occurs within the trachea unless the inhaled air, or more especially inhaled oxygen, is adequately wetted. For the ordinary patient breathing air through the tracheostomy tube an improvised steam bottle device can be used or better still a pump specially designed for the purpose. If oxygen is fed directly to the tracheostomy it can be passed through a suitable nebulizer like that designed by Wright (1958), which gives a mist so fine that it is carried like a gas along rubber tubing. Such a device is cheap and compact, can be used to give antispasmodic drugs in the aqueous aerosol if they are indicated, and is most effective provided inlet and outlet are connected the right way round. (The device was demonstrated.) When artificial mechanical ventilation is used, adequate wetting of the inhaled gas is even more important. Fortunately most mechanical respirators now have a wetting device built in.

(2) *The Prevention and Treatment of Infection*

The need to sterilize the tubing used for sucking secretions has been mentioned. The physiotherapist can also play an important part in the prevention and treatment of localized pneumonia by suitable postural drainage and movement of patients. Lastly, there is the role of antibiotics. With the ever-increasing risks from antibiotic resistance among bacteria, mainly staphylococci, it is desirable particularly in hospitals not to use antibiotics needlessly or routinely. "Prophylactic" use in patients with tracheostomy for such conditions as barbiturate poisoning and poliomyelitis is to be deprecated. But antibiotics are important in the treatment of the chronic bronchitic patient with respiratory failure who has a tracheostomy. The choice of suitable antibiotics is a wide subject, but in many elderly patients who have hæmophilus infection chloramphenicol has much to recommend it (Douglas *et al.*, 1957).

(3) *The Provision of Adequate Ventilation*

Detection of hypoventilation.—Whenever the ventilation of the lungs becomes inadequate for the metabolic requirements of the patient respiratory failure occurs with a rise of carbon dioxide and a fall of oxygen tensions in the arterial blood. This, indeed, may well have been the reason for the tracheostomy. The tracheostomy alone may have rectified the trouble by removing obstruction to the airway and by decreasing the anatomical dead-space so that for a given total ventilation there is a relatively greater alveolar ventilation. But in many cases artificial ventilation through the tracheostomy may be necessary because hypoventilation is still present. It is most surely detected by measuring the carbon dioxide content either in the arterial blood or in the expired alveolar gas. Fig. 1 shows

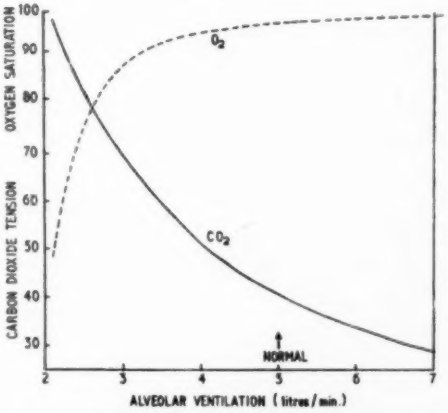

FIG. 1.—The relationship between alveolar ventilation and arterial blood oxygen saturation on carbon dioxide tension.

that it cannot readily be detected by the appearance of cyanosis. With arterial tension of carbon dioxide and oxygen saturation plotted on the same axis against alveolar ventilation it will be seen that, at a normal alveolar ventilation of say 5 litres per minute, the arterial dioxide is about 40 mm. and the oxygen saturation 97%. If the ventilation falls by almost 50% to 3 litres the carbon dioxide rises to 70 mm. yet the saturation is still about 85% and many observers cannot detect cyanosis till the saturation is below 80% (Comroe and Bothelo, 1947). At this saturation

the oxygen tension is down from the normal 100 mm.Hg to about 60 mm.Hg and the patient is seriously anoxæmic. Thus cyanosis is a most insensitive test of hypoventilation and anoxæmia, not only because of difficulty in its detection but because the shape of the oxygen dissociation curve means that a low oxygen tension is reached before there is much of a drop in saturation. Unless polycythæmia or other complicating influences are present central cyanosis should be regarded as indicating not a lack but gross lack of oxygenation. Measurement of arterial carbon dioxide, which faithfully reflects the adequacy of ventilation, should be practicable in any reasonably equipped hospital, for it is in "oligopnœa" (inadequate air-output from the lungs) what measurement of urea is in oliguria (Hugh-Jones, 1958). And few think of dealing with renal insufficiency without using the blood urea as a guide.

Oxygenation and ventilation.—Oxygen can readily be supplied by passing the gas, wetted, directly into the tracheostomy. This procedure is useful whenever there is a chance of anoxæmia but will not remove excess carbon dioxide. Artificial mechanical ventilation is the only satisfactory procedure if hypoventilation is at all severe, and is essential in many cases of poliomyelitis, tetanus and barbiturate poisoning. The same applies in severe cases of acute respiratory failure in chronic chest disease, though here oxygen administration with stimulation of ventilation by adequate doses of analeptics such as nikethamide may suffice.

Whenever artificial ventilation is required, a cuffed tracheostomy tube should be used and the volume of air exhaled by the patient recorded. If this is done the ventilation needed by the patient can be quite well found, without carbon dioxide measurements, from tables giving the patient's needs in relation to his size. Patients with chronic chest disease are an exception; in them carbon dioxide measurements are very helpful in gauging the ventilation needed, since their dead-space may be increased from areas of the lung being ventilated but not perfused with blood, and the overall ventilation required to give a correct alveolar ventilation may differ considerably from that in subjects whose lungs are normal.

Dangers of over-ventilation.—Ventilation should be adequate but not excessive. Acute over-ventilation may cause a progressive fall in blood pressure if venous filling of the heart becomes inadequate. Chronic over-ventilation may make it very difficult to wean the patient from the pump because his respiratory centre becomes acclimatized to a low carbon dioxide tension. This is especially dangerous for poliomyelitis patients in whom over-ventilation is often more of a problem than under-ventilation.

[A film was shown to demonstrate some points about artificial mechanical ventilation in a patient with a tracheostomy.]

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Mr. Angell James emphasized the following technical points:

(1) Operation should be performed early to avoid venous engorgement.

(2) The trachea should be entered as low as possible to avoid subsequent subglottic stenosis, and it is usually best to divide the isthmus of the thyroid.

(3) The opening in the trachea should be circular, and in a permanent tracheostomy as after laryngectomy the edge of the trachea should be sutured to the skin.

(4) There should be no tension on the trachea and if necessary some of the manubrium sterni may be excised.

(5) Epithelial ciliary action should be preserved as far as possible by humidifying the inspired air and using only the softest suction tube that is feasible.

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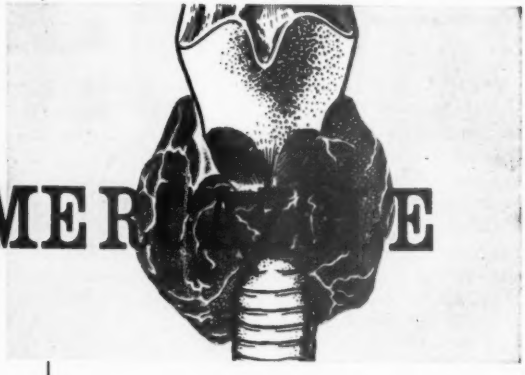

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Section of Laryngology

President—R. L. FLETT, F.R.C.S.

Meeting
December 5, 1958

PAPERS were read as follows:

Osteomyelitis of the Superior Maxilla in Infants. Mrs. FLORENCE CAVANAGH.

Discussed by Mr. R. G. MACBETH, Mr. J. C. HOGG, Mr. P. A. THORPE, Mr. E. D. D. DAVIS.

Destruction of the Superior Maxilla in Felty's Syndrome.—Mr. R. F. MCNAB JONES (for Mr. J. W. COPE).

Chondroma of the Nasopharynx.—Mr. P. TIMMIS (for Mr. F. C. W. CAPPS).

Orbital Cellulitis with Neurological Complications.—Mr. P. C. LEESON (for Mr. N. ASHERSON).
Discussed by Mr. H. V. FORSTER, Mr. C. GILL-CAREY, Mr. F. C. W. CAPPS, Mr. N. ASHERSON, THE PRESIDENT.

Mrs. Cavanagh's paper will be published in the *British Medical Journal* and the other three papers in the *Journal of Laryngology*.

Meeting
February 6, 1959

DISCUSSION ON BLOCK DISSECTION OF THE NECK

Mr. J. I. Munro Black (Newcastle upon Tyne): Block dissection of the neck was originally suggested as the most satisfactory method of dealing with cervical node metastases from a primary malignant lesion in the mouth, throat or upper respiratory tract. The first consideration had been surgical extirpation of the primary lesion and a stage was reached when this could in many cases be done with reasonable hope of success. Even though the primary lesion did not recur *in situ* eventual failure often occurred owing to deposits in the lymph nodes of the neck. Surgical extirpation of these involved lymph nodes offered lasting success in many cases, but some failures occurred owing to more widespread deposits. It became evident that the extent in area of invasion was often much wider than was thought, and that the greatest hope of success lay in removal of the whole possible lymph-node-bearing tissues of the neck, or side of the neck involved. This meant from the mid-line in front to the trapezius muscle behind, and from the mandible above to the clavicle below. All non-essential tissues were removed *en bloc* including the sterno-mastoid muscle and internal jugular vein. The submandibular triangle was cleared and the posterior belly of the digastric muscle removed as well. Often the lower pole of the parotid gland was removed and usually the spinal accessory nerve had to be sacrificed.

Nothing less than this extensive removal of tissues was considered safe. At this stage of progress things were fairly clear cut and the accepted best hope of cure for the patient was surgical extirpation of the primary growth and block dissection of the corresponding side of the neck. The necessary features which justified this proceeding were:

(1) The primary lesion must have been excised or be excisable with expectation of no local recurrence.
(2) Actual or likely metastasis in the cervical lymph nodes.
(3) No distant metastases.
(4) A patient fit to stand the operation.

The first and most important factor was the nature, situation and extent of the primary lesion. If it could not be removed nothing further could be done. On the other hand it was known that not all primary lesions had the same tendency to spread to the neck nodes and doubt arose regarding possible anticipation of such by operation on the neck. Carcinoma of the tongue was most likely to metastasize at some time, and the suggestion was made of doing a block dissection of the neck before any clinically detectable enlarged glands were found. This was the so-called prophylactic block dissection and occasioned many differences of opinion. It was urged by some as offering a definite improvement in ultimate cure rate—especially in view of the known occasional long latent period between cure of the primary lesion and eventual neck gland metastasis. Others have thought it safe enough to follow up the patient at regular and frequent intervals, doing a block dissection at once if any enlarged neck glands were detected. Such regular follow-up examinations are now, or should be, routine in all cases of malignant

disease, and it seems that prophylactic dissection is not now so popular.

Carcinoma of the lip had a much less tendency to metastasize and a prophylactic block dissection was not justified. By some it was considered unnecessary even to perform a full dissection, but to limit this to the upper part of the neck.

On the other hand, there were some anaplastic lesions which had a small and easily removable primary source, but which metastasized early and in which it was a waste of time excising the lymph nodes, because recurrence and spread would occur in any case.

The management of these cases next became complicated by the possibility of using radiotherapy as a means of dealing with the primary lesion, and gradually this has tended to supplant surgical extirpation, except for those of little radio-sensitivity. Probably the usual initial attack upon the primary growth will be by radiotherapy of some type. Only where this is known to be likely to fail will operation be suggested. Some such cases are again determined by the type or extent or perhaps situation of the primary growth. For instance, advanced bulky intrinsic growths of the larynx, especially with subglottic spread, do not do well with irradiation, nor does post-cricoid carcinoma; elsewhere, radiotherapy may be the only hope in the highly anaplastic lesion.

It is, then, difficult to separate block dissection of the neck, as a subject for consideration, from the primary lesion which is the really important thing. Perhaps a feeling is growing that in a majority of cases the primary lesion can be dealt with by irradiation, either from a distant source or by local implantation: or by surgical excision. Consideration of the failures may have suggested that metastasis to the cervical lymph nodes was responsible, and perhaps ultimate success in more cases might be achieved by block dissection as a necessary part of the treatment.

Again, consideration must be given to the primary lesion because certain characters may suggest the likelihood or otherwise of lymph node metastasis. These are:

(1) *The situation of the primary lesion.*—For instance, a carcinoma of the tongue is a very likely source for lymph node metastasis, and block dissection plays a definite part in its management. Not so carcinoma of the lip, nor intrinsic carcinoma of the larynx.

(2) *The type of the primary lesion.*—An anaplastic carcinoma or lympho-epithelioma is very likely to metastasize easily, and block dissection may be possible, but more likely to achieve cure will be radiotherapy.

(3) *Duration of the primary lesion.*—The advanced lesion of any type or situation will probably have metastasized. Progression to this advanced stage may depend upon an obscure situation of the lesion or delay in presentation of the patient for some other perhaps social or personal reason.

(4) *The position of the primary lesion* may be such that treatment by radiotherapy from a distant source may include, and in fact be through, the region of possible glandular metastasis. This applies particularly to the larynx and its immediate surroundings, and does simplify the issue. If the primary lesion, and incidentally the likely region of lymph node metastasis, has been irradiated, then any residuum or recurrence of the growth will have to be excised, and as far as the lymph nodes are concerned I believe a full block dissection to be the correct operation. Irradiation of a lymph-node-bearing area seems to have some sealing effect and it is unusual to get a new metastasis in such an area, but a metastasis may find its way around it to a more distant node. So it is not unusual to find a deposit in a lymph node high up the neck from a postcricoid carcinoma.

I have myself tended to accept this concept of treatment and for some time tested it by trying it as it applies to the larynx and its immediate surroundings, i.e. aryepiglottic folds, epiglottis and pyriform fossa; but not postcricoid carcinoma. I have no decided views about this latter lesion, and confess almost despair.

Deep X-ray therapy, perhaps of the megavolt variety, is used as the primary attack, even in advanced cases where it is almost thought unsuitable, and then surgical excision for any residuum or recurrence. I justify excision only of what is present—the primary lesion only, block dissection of neck glands only, or both together if necessary. All cases taken for treatment are followed up at regular and frequent intervals.

The most likely present indications for a block dissection of the neck are:

(1) *Failed irradiation.*—This applies when treatment to the primary lesion has been through the area of likely glandular metastases. If the primary lesion is healed and enlarged glands present, then block dissection alone is done. If the primary lesion is not healed, then it must be removed as well, which usually means laryngectomy. I do not justify prophylactic block dissection in the absence of palpable glands.

(2) *Unsuitability for irradiation.*—Cases where the primary lesion is not suitable for irradiation, especially very advanced intrinsic carcinoma of the larynx, but in which the primary lesion can be excised by operation.

(3) *Primary lesion distant from the neck.*—Cases where the primary lesion has been cured

by irradiation but is distant from the neck. Operation will not be wise in the highly anaplastic carcinoma, but the neck glands in such a case should be curable by irradiation.

There remain some alternatives for discussion, such as the possibility of treating the neck gland metastases by irradiation. There is no doubt that irradiation can cure such a lesion, and where the primary and a palpable gland lie in the same field of irradiation I believe that is the method of choice. If the primary and that neck gland are apparently cured, but a new gland appears outside the field of initial irradiation, then I believe it is justifiable to attempt cure of it also by similar irradiation, and I believe with expectation of success.

The other problem is whether block dissection of the neck as a part of treatment will enhance the end-results in cases where we are failing to cure the patient. I feel that this is particularly applicable to postcricoid carcinoma, which will be discussed by Mr. Shaw. There is but one point which I believe to be of importance, and that is that when we fail, it is the very first evidence of failure which is important, and that may lie in a characteristic of the primary lesion, not in the eventual occurrence of lymph-node metastasis. It is no use hoping to improve results by performing block dissection if failure is predetermined by local recurrence of the primary lesion or distant metastasis.

Mr. H. J. Shaw (London):

It is my intention to examine and discuss certain aspects of the modern philosophy pertaining to block dissection of the neck, to present the material studied and to give the end-results of a recent consecutive series of 93 patients undergoing radical block dissection of the neck. The operations were all performed in the course of treatment for squamous carcinoma involving the extrinsic larynx and laryngopharynx by the surgical staff of the Royal National Throat, Nose & Ear Hospital during the period 1952–1958.

Principles, Definition and Extent

In contrast to some other types of cancer, the behaviour and natural history of squamous carcinoma of the upper air and food passages is fairly well known and is predictable to a considerable extent, especially in the well differentiated majority of lesions. There is step by step progression, usually with definite delays, as the disease slowly advances from primary to regional lymph nodes and later to the blood stream. It is this relative predictability of spread with the delay between nodal metastasis and blood stream dissemination of which it is necessary to take full advantage when treating cervical metastatic cancer. As a corollary, the fact that the majority of squamous carcinomas of the head and neck region will remain confined above the level of the clavicles even during the terminal stages of illness has already received much emphasis (Braund and Martin, 1941; Martin *et al.*, 1951; Copeland, 1955; Pietrantoni and Fior, 1958).

Curative operations for cancer are still based on the main principle of a block resection of normal tissues surrounding a lesion. Therefore the best chance of eradicating the disease once it has metastasized to the cervical lymphatics is to carry out radical block resection of the relatively closed system of principal lymph node groups with all their supporting tissues, sparing only the vital structures. Block dissection of the neck may then be defined as the surgical removal of a large block of neck tissues to include the maximum amount of accessible cervical lymphatics within which are contained deposits of secondary metastatic carcinoma, leaving an adequate margin of normal tissue on all sides.

Since these lymphatics are very extensive and closely linked, the block of tissue removed must reach from mandible to clavicle between the superficial and the prevertebral fascia, and from the mid-line anteriorly to the leading edge of the trapezius muscle posteriorly. This includes most of the contents of the submental, the submandibular, the anterior and posterior triangles of the neck. At very least the sternomastoid and omohyoid muscles, the internal jugular vein, the submandibular salivary gland and the tail of the parotid salivary gland, together with all related lymphatic and supporting tissue must be removed.

Most authorities agree that it is also necessary to sacrifice the spinal accessory nerve in order to be sure of a complete clearance of lymphatics at the skull base and in the posterior triangle (Martin, 1957; Beahrs *et al.*, 1955). Others, also with wide experience, feel strongly that its posterior branch to the trapezius muscle may be safely spared in elective neck dissection and especially when bilateral operations are undertaken (Bocca, 1953; Ward and Hendrick, 1950; Pietrantoni and Fior, 1958).

For many years there has been a tendency to favour certain less radical or partial block dissections of the neck, particularly for cancer of the lip and floor of the mouth. This has been due to a supposedly limited area of possible lymphatic involvement in these cases, and to a desire that patients might therefore be spared some of the risk and disability resulting from the more radical operation, while retaining an equally good post-operative prognosis. They may be unilateral or bilateral and in most cases

are effected with preservation of the internal jugular vein, sternomastoid muscle and spinal accessory nerve (Brown and McDowell, 1944; Meyer, 1950). It seems to me that such compromise procedures are to-day unwise and unsafe in almost all cases where greater security may be gained at no more risk by the use of the radical operation.

It is even more necessary to avoid such an ill-conceived and dangerous manœuvre as "clearing out glands" along the carotid sheath at the time of opening the neck for resection of a primary lesion. There should be no room for half-measures of this type. Even the traditional procedure of open biopsy of a neck node should be avoided if possible, a frozen section examination with the intention to proceed if necessary to immediate radical neck dissection being preferable.

Compromise with cancer may prove fatal for the patient. It is surely better to offer him the best chance of permanent cure with a radical neck dissection and slight, but acceptable disability, than to risk death in return for the price of complete functional integrity.

Indications and Applications: "Elective" and "Essential" Neck Dissection

The decision to carry out radical block dissection of the neck must rest upon the merits of each case and has been based upon the following general rules:

(1) There should be clinical evidence that cancer is present in the cervical lymphatics.
(2) The primary lesion should have been controlled or it must be possible to remove it in continuity with the cervical lymphatics by a combined operation.
(3) There must be a reasonable chance of complete removal of the disease.
(4) Surgery should offer a more certain chance of cure than other methods.

In recent years, many surgeons of experience have realized that some exceptions should be made to the first of these indications. It has been shown statistically that for cancer involving the extrinsic larynx and laryngopharynx, the likelihood of clinically undetected metastatic disease being present in the cervical lymphatics is so high, and the risks of awaiting clinical evidence of it are so great, that what has been termed "prophylactic", or better, "elective" or "immediate" radical neck dissection is necessary. To adopt a "wait and feel" policy in these cases will certainly invite many failures (Ogura and Bello, 1952; Lewis, 1953; Ormerod, 1954; Ogura, 1955; Kuhn *et al.*, 1957).

Further support for this "Life Insurance" policy (Dargent, 1953) is provided by the necessity of entering the neck for resection of the primary tumour in many cases, especially in cancer of the cervical viscera. It is at this time comparatively simple to extend the field of operation to include neck dissection, whereas the inevitable disturbance and scarring of the first operation may compromise the result at some future date when metastases are palpable and neck dissection becomes "essential".

I therefore wish to emphasize that radical neck dissection should be considered clinically "essential" when evidence of operable disease is palpated in the cervical lymphatics; and that it should be termed "elective" in the absence of these findings, when in the judgment of the surgeon concerned impalpable cervical metastases may already be present.

The application of the elective principle to mid-line lesions is often questioned, but if every case is first carefully weighed on its merits, the same principles must surely hold, although there would seem less cause to be dogmatic as to whether a bilateral dissection should be simultaneous or staged.

For these reasons and because of the necessity for having complete control of the primary lesion, it would seem most logical to advise elective dissection chiefly in cases where surgical resection of the primary tumour is considered the more suitable treatment. The operation should then be carried out as a combined procedure. In the present series just under half or 42 of the dissections were elective, whereas 59 were essential (Table II).

In early lesions of the mouth, pharynx and larynx where irradiation may be the first choice of treatment, it is certainly necessary, when the primary is controlled, to await the classic indications for an essential neck dissection. But when there is a recurrence at the primary site after irradiation, it will be safer in many cases to carry out a resection of the primary combined with an elective radical neck dissection.

It is really necessary to cease thinking of cancer of the pharynx and extrinsic larynx in terms of local disease requiring local treatment. It should be clear that what is a regional disease needs regional treatment for success.

Contra-indications to the operation are well known but may be listed as follows:

(1) Complete fixation of metastatic disease to the deep neck structures or skull base.
(2) Clinical or radiological evidence of distant metastases.
(3) Advanced senility.
(4) Coexisting disease soon likely to be of itself fatal or likely to result in very grave operative risk.

Modern surgical developments have even

made it possible to contend that some exceptions can be made to the second contra-indication. A single small metastasis in a peripheral lung field which may be resectable or which may well be slow growing and comparatively symptomless, may not necessarily or of itself preclude neck dissection or combined resection of neck lymphatics with the primary lesion. And in certain circumstances it can be argued that the operation, even when of necessity incomplete, may have definitive palliative value, providing closure and primary healing of the wound can be expected.

Furthermore, it is important that chronological age alone should not be an absolute contra-indication to surgery as patients in the later decades of life stand such operations surprisingly well. When a physician is requested for his opinion on the patient's medical status, he should not be asked to state merely whether the patient is fit for surgery, but rather when and by what means he may be made fit for the operation. If the former attitude is adopted in requesting a consultation, the cautious physician who is unused to these cases may jeopardize their chance of cure by a decision against operation.

Once the decision for operation has been taken there should be no delay.

Extended Procedures

(1) *The combined operation.*—To-day it is being increasingly demonstrated that for all except the smaller laryngeal and laryngopharyngeal lesions without clinical metastases, the best chance of an initial cure lies in early radical resection. If clinical evidence of operable and homolateral neck metastasis is present, an "essential" neck dissection with combined resection of the primary tumour should be performed. Such combined operations must always include immediate one-stage functional reconstruction whenever possible (Conley, 1953; Shaw and Ormerod, 1957). The same policy of *en bloc* combined resection is applicable on an "elective" basis even if no metastases are clinically detectable in the neck; particularly to large or extensive but operable tumours of the mouth, the oropharynx, the laryngopharynx, and the extrinsic larynx (Figs. 1 and 2); (Barclay *et al.*, 1951; Reed, 1956; Shaw, 1957; Pietrantoni, 1958).

In performing combined resection for many tumours of the cervical viscera it is also necessary to extend the area of neck dissection to include *en bloc* removal of the hyoid bone, pre-epiglottic space, strap muscles and paratracheal lymphatics together with partial or even total thyroidectomy. This is due to the ease and high frequency with which direct and metastatic spread of disease to

FIG. 1.—Large carcinoma of left pyriform fossa resected by radical combined operation.

FIG. 2.—Patient two weeks after removal of specimen in Fig. 1.

these tissues takes place, particularly in tumours of the laryngopharynx and cervical œsophagus (Shaw, 1957; Raven, 1958). These sinister methods of spread also lend especial emphasis to the need for combined elective neck dissection in many such cases. Before operation, it is frequently impossible to detect involved paratracheal nodes or areas of direct spread through the wall of the laryngopharynx. If operation be delayed until such metastases are large and palpable, the case may well be inoperable owing to carotid and deep neck tissue involvement or mediastinal extension.

It is also becoming clear that this policy will not significantly increase operative or post-operative mortality if carried out by a skilled

team. Pietrantoni and Fior (1958) reporting 570 consecutive cases of laryngeal and hypopharyngeal cancer give an operative mortality of only 2·7% in patients subjected to total laryngectomy with mono- or bi-lateral neck dissection. In their impressive experience they state that "laryngectomy combined with neck dissection carries no higher operative risk than total laryngectomy alone". In the present series of 93 patients a post-operative mortality of 6 is recorded. This is not greater than that in another series of 95 patients subjected mainly to total laryngectomy or pharyngolaryngectomy alone (Ormerod and Shaw, 1956).

(2) *The bilateral operation.*—Radical block dissection of both sides of the neck in the same patient has been performed as a two-stage procedure for many years, with the customary preservation of one internal jugular vein due to the fear of fatal cerebrovascular complications. However, although Crile reported a successful case of bilateral neck dissection with removal of both internal jugular veins in 1906, only in the last decade has it been shown that such extensive operations are possible in one stage without increased mortality, but with occasional increased morbidity (Moore and Smith, 1951; Perzik, 1953; Bocca, 1953; Ogura and Bello, 1952; Martin, 1957).

In view of this knowledge few will to-day dispute the propriety of an "essential" bilateral neck dissection, the indications and technique being basically the same as for the unilateral operation. But a point of difference in experienced opinion is reached whenever an "elective" bilateral neck dissection has to be considered. The majority are in practice still opposed to such heroic measures, although from the strictly logical viewpoint it may be argued that it is in the best interests of the patient to perform such an operation for certain of the larger mid-line tumours of the pharynx and larynx (Bocca, 1953; Pietrantoni, 1958). However, a possible compromise may be achieved by careful assessment of the primary lesion and the performance of an elective combined unilateral neck dissection on the side mainly involved by the primary lesion (Fig. 3) (Ogura, 1958).

When both internal jugular veins are removed simultaneously it is true that the alternative venous pathways seem to be inadequate in a small percentage of individuals, and consequently certain cerebrovascular disturbances together with gross and persisting œdema of the superficial tissues of the head and upper neck have been noted in a few cases (Bocca, 1953; Frenckner, 1958).

There is also a difference of opinion as to whether it is in fact necessary to sacrifice both

FIG. 3.—Squamous carcinoma of left supraglottic region crossing mid-line on laryngeal surface of epiglottis.

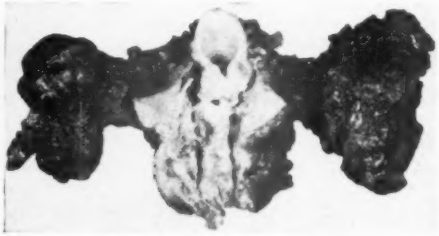

FIG. 4.—Extensive carcinoma of cervical œsophagus. Bilateral combined operation with preservation of left internal jugular vein.

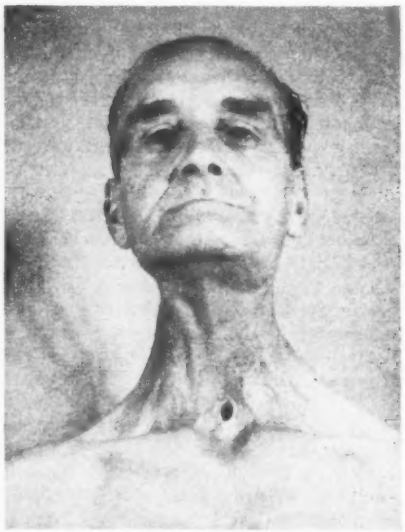

FIG. 5.—Patient six weeks after removal of specimen in Fig. 4.

internal jugular veins, and it is felt by some authorities that careful stripping and preservation of the vein on one side may be safely practised (Ormerod, 1954; Barbosa, 1956; Pietrantoni, 1958). This does seem an acceptable safety measure, especially in laryngopharyngeal cancer, providing the dissection is elective on the side where the vein is to be spared. In fact this procedure has been followed in 5 of the 8 cases to be reported in the present series (Figs. 4 and 5).

No serious complications were attributable to bilateral resections although in one case of bilateral simultaneous radical neck dissection with resection of both internal jugular veins and total laryngectomy, marked cyanosis and œdema of all the soft tissues of the head and upper neck developed post-operatively with severe headache and discomfort on lying down. The swelling and discomfort gradually subsided over a period of six months.

Unfortunately, there is at present no certain means which can be used to test the efficiency of the collateral venous return from the head, but before carrying out elective neck dissections, especially if bilateral, it would seem prudent to assess the approximate internal jugular status of the patient by a simple skull base X-ray, as proposed by Frenckner (1958).

Operation after Irradiation

After recent irradiation, and provided an interval of four to six weeks is allowed between the two types of treatment, additional technical difficulties are seldom encountered. However, after a period of about six months from the end of irradiation, progressive fibrotic and other degenerative changes in the normal neck tissues begin to cause an increasing degree of troublesome adhesions in tissue planes, with fibrosis in the soft tissues themselves. Some degree of excess hæmorrhage may also be encountered due to loss of retractability and contractility of the smaller blood vessels. The extent of such changes is roughly in direct proportion to the length of time elapsed between irradiation and surgery.

Other variables such as the type of irradiation, filtration factors and total dosage, together with the skill of administration and the indeterminate factor of the individual biological reaction, may also greatly affect future surgical treatment and subsequent healing. Nevertheless, it has been found repeatedly that the least operating difficulties or subsequent complications follow the skilful use of teleradium or telecobalt irradiation in full doses, compared with the more "traumatic" use of conventional 200–250 kV high voltage therapy (Mill, 1956). In fact the optimum range for irradiation of most forms of head and neck cancer lies between 1 and 5 MeV, both from the viewpoint of immediate results and possible later surgery (Lederman, 1956).

Special care must be taken in assessing the value of radical block dissection in patients who have had more than one course of irradiation to the neck. Many difficulties may be encountered in this type of case, the most serious being a complete failure of healing in the deeper neck tissues rather than actual necrosis of skin or wound edges.

Material of Present Series

A total of 132 operations of radical block dissection of the neck were carried out by the surgical staff of the Royal National Throat, Nose and Ear Hospital during the period 1952–1958 inclusive. In all, 93 patients underwent radical neck dissection at some time during the course of treatment for squamous carcinoma of the extrinsic larynx and laryngopharynx. There were 85 unilateral dissections and 8 patients were submitted to bilateral operation, 4 of the latter being simultaneous resections and 4 staged at intervals.

As expected, sex incidence showed a large preponderance of 70 males to 23 females, the latter group consisting mainly of 19 patients with the annular postcricoid type of cancer. The overall median age was 57, ranging from 28–73.

Histopathology

Clinically positive cervical lymph nodes were found in 40 of the 93 patients (43%) at first attendance. It is highly significant that a further 27 developed positive nodes after treatment and control of their primary lesions (Table I.)

TABLE I.—RELATION OF PRIMARY TUMOUR SITE TO CLINICALLY POSITIVE CERVICAL METASTASES

Primary site	Total cases	Unilateral nodes at first attendance	Bilateral nodes at first attendance	Nodes appearing after control of primary
Epiglottis	9	2	2	2
Aryepiglottic folds and arytenoids	18	7	—	4
Ventricular bands	29	9	—	10
Pyriform fossæ	18	10	—	5
Postcricoid area	10	5	1	2
Posterior and lateral walls	9	4	—	4
Totals	93	37	3	27

TABLE II.—TOTAL NUMBERS AND END-RESULTS OF RADICAL NECK DISSECTION ACCORDING TO CLINICAL APPLICATION

	1952	1953	1954	1955	Total	Alive and well (minimum 3 years)	1956	1957	1958	Total	Alive and well (December 1958)
Elective ...	1	0	5	9	*15*	*13*	8	9	10	*42*	*34*
Essential ...	5	6	11	12	*34*	*7*	6	10	9	*59*	*15*
Combined ...	3	2	12	18	*35*	*18*	12	17	18	*82*	*46*
Simple ...	3	4	4	3	*14*	*2*	2	2	1	*19*	*3*
Totals: ...	6	6	16	21	*49**	*20*	14	19	19	*101**	*49*

* These figures include 2 and 8 bilateral operations respectively.

Careful examination of specimens from 59 essential block dissections of clinically positive necks revealed 8 (13·5%) whose nodes were histologically negative for cancer. The size of this error is perhaps no larger than might reasonably be expected.

However, it was of greater interest and significance to find that examination of nodes in the specimens of 42 elective block dissections revealed a total of 19 (45·2%) which were histologically positive for metastatic carcinoma. Allowing for even a small false negative error, this probably means that over half the clinically negative necks contained metastatic cancer.

Histological evidence to support the known increase in clinical aggressiveness of cervical secondaries was found. Approximately 40% of the well-differentiated primary lesions which developed cervical metastases gave rise to poorly differentiated carcinoma in the neck nodes. This may provide an additional reason for early elective neck dissection before the firm establishment of palpable and possibly undifferentiated cervical secondaries.

Multiple primary cancer was noted in 6 patients (6·4%); two basal cell carcinomas of facial skin, one on the right anterior faucial pillar, one in the right thyroid lobe and two in the main bronchi, the latter two accounting for the deaths of patients free from their laryngopharyngeal tumours. The presence of half of the second primary cancers in other parts of the air and upper food passages, and thus systemic in distribution, corresponds with findings in a recent survey of this subject (Epstein and Shaw, 1958).

End-results

In Table II is set out an analysis and comparison of the three-year and up-to-date results of four different clinical applications of the operation in 93 patients with cancer of the extrinsic larynx and laryngopharynx treated at some stage by radical block dissection during 1952–1958. The terms "combined" and "simple" refer to whether the neck dissection was combined with total laryngectomy or pharyngolaryngectomy, or whether it was performed as a separate simple procedure. The latter cases were all in fact essential dissections.

It will be seen at once that the elective and combined procedures were easily the most successful in terms of survival; whereas reliance on essential or simple neck dissection did not result in anything greater than a 20% three-year survival rate.

All patients undergoing radical block dissection during the four-year period 1952–1955 and numbering 47 are included in Table III for complete analysis. A net three-year recurrence-free rate of 45·4% is obtained, represented by 20 three-year survivors out of a determinate total of 44 patients. If the least successful postcricoid and posterior wall group of tumours are omitted from the total, the three-year rate rises to 52·3%.

TABLE III.—PATIENTS WITH SQUAMOUS CARCINOMA OF THE EXTRINSIC LARYNX AND LARYNGOPHARYNX HAVING RADICAL NECK DISSECTION IN THE COURSE OF TREATMENT (1952–1955)

Total number of patients			47
Indeterminate results:			3
Lost track of without cancer		0	
Dead from other causes without recurrence ...		3	
Determinate results (to December 31, 1958)			44
(*a*) Failures:			24
Dead as a result of cancer		19	
Dead as a result of operation		3	
Dead from other causes with recurrence ...		1	
Alive with recurrence		1	
(*b*) Alive and well—recurrence-free after three years ...			20

Absolute minimum three-year recurrence-free rate: 20/47 = 42·5%.
Net three-year recurrence-free survival rate: 20/44 = 45·4%.

Although these results are not easily comparable with others, the totals being small and representing only a three-year survival rate, it is felt that they do represent a trend towards an improved prognosis for such patients. This is perhaps apparent when these results are compared with a net five-year recurrence-free rate of 19·3% for 117 patients with similar tumours treated at the same centre along similar lines but without radical block dissection, during the period 1947–1951 (Shaw, 1957).

Of the total of 47 patients, 19 had received their primary treatment by irradiation, had developed recurrences and were secondarily treated by radical surgery including neck dissection. Of these, 7 survived alive and well for a

minimum three-year period and there were 12 failures. Conversely it should be carefully noted that all 10 patients treated initially by radical surgery and who developed obvious clinical recurrences, died of disease despite irradiation in full doses.

In their recent extensive report Pietrantoni and Fior (1958) have shown that their five-year survival rate is more than doubled when elective neck dissection is combined with total laryngectomy, compared with the results of total laryngectomy and essential neck dissection. It might seem that such findings are supported by the trend of recurrence-free survival demonstrated in the present series.

Conclusions

(1) Block dissection of the neck must be radical in extent.

(2) Indications to-day are wider. Elective radical neck dissection is justifiable and necessary in many cases.

(3) Combined operation is likely to give the best results in larger tumours of the pharynx and larynx.

(4) Bilateral radical neck dissection is safe and frequently necessary for mid-line primary lesions.

(5) Radical neck dissection after modern irradiation techniques is practicable and gives many salvages.

(6) An interim report on 47 patients having radical neck dissection in the course of treatment for squamous carcinoma involving the extrinsic larynx and laryngopharynx gives a net three-year recurrence free survival rate of 45·4%.

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Mr. Maxwell Ellis (London):

Definitions.—The title of this debate, block dissection of the neck, is the name first given by Crile (1906) to a wide excision of the lymphatic tissues of the neck in one block or piece, as opposed to a piecemeal or partial procedure. By an *en bloc* excision most of us mean an excision of the primary growth together with a block dissection of the neck, in cases where metastases are demonstrable. The term prophylactic has been applied to both these procedures where no lymphatic metastases have been demonstrated before or at operation, and is thus used in its usual and grammatical connotation. I do not like the term "elective", which was recently coined in America, because it seems to me to lend a sense of compulsion to the procedure, and by its very name almost to persuade one in its favour. Not only is the term beguiling, but I submit it is inaccurate. Somebody may elect to do what someone else would elect to refrain from doing. I therefore believe that the word "elective" somewhat detracts from clarity and may introduce unnecessary emotions, as I freely confess it has in me, and I hope its incipient use will disappear.

For similar reasons, and more strongly, I am averse to the term "essential", even when applied to the simplest surgical procedure, but especially in this field where conceptions are still fluid and certainty still remote.

Lymphatic spread of cancer.—I am not quite sure how the vogue for prophylactic *en bloc* excision arose, and the rationale on which it is

based may stem back to the permeation theory of spread associated originally with breast cancer. Most of the present protagonists of the combined operation seem to quote Ogura (1951), but although he stresses often finding growth in nodes which were not previously palpable, he does not mention the intervening tissues at all. In any event, he advised the operation only for advanced primary lesions of the laryngopharynx.

Early views.—When in a predicament of principle, I have usually found it immensely helpful to go back into the history of the particular matter. I therefore re-read Crile's (1906) paper on block neck dissection. I had recalled this paper as the first reasoned account of the technique, advocating especially excision of the sternomastoid muscle with the internal jugular vein. In fact, however, the paper is much more comprehensive, containing a discussion also of principles of treatment. Crile believed, what has been implied earlier in this discussion, that the cancer spread by permeation of the lymphatic vessels to the regional nodes, and that when these became full of growth it overflowed along other lymphatic trunks, although remaining confined within an accessible lymphatic collar for a long time. When nodes were not palpable, he practised excision of the primary focus together with the regional lymphatic drainage system, in other words what would now be called by some surgeons "an *en bloc* prophylactic excision with limited neck dissection". When nodes were palpable, he excised the primary growth together with a wider, more radical neck dissection to remove all the lymphatics on that side of the neck, that is, what we now call an *en bloc* excision. He maintained that excision of the primary growth alone is "unsurgical". Our "new" approaches were thus Crile's routine practice sixty years ago, for he began these procedures in 1898, and with true American liberality was able in 1906 to report on no less than 132 cases of cancer in the mouth, pharynx and larynx, and in the salivary and thyroid glands.

Another side of the picture was displayed by Butlin and Spencer (1900), the former of whom laryngologists will know as a pioneer in this country of laryngeal surgery. Butlin and Spencer did not accept the theory of spread by permeation, and believed that the nodes were invaded by emboli of cancer cells. They quoted Heidenhain as having demonstrated this method of spread (Heidenhain was also quoted in a similar connexion by Halsted writing on carcinoma of the breast). Carrying the argument further they maintained that there was no question of just one set of nodes being involved, but that the chain of nodes along the internal jugular vein must be considered as a whole. Butlin and Spencer therefore advocated excision of the whole chain of nodes in the anterior triangle of the neck (a radical or block dissection as it was then understood) whether or not they were palpable, but at a separate operation, as soon as possible after excision of the primary growth. They felt that there was little risk of leaving cancer in the tissues between the primary site and the nodes, owing to the embolic manner of spread. Brewer (1923) quoted Beckman in the same strain, stating that Beckman treated a number of mouth cancers by an *en bloc* primary and lymphatic excision, and failed to find cancer cells in the tissues between the primary and the nodes. Brewer added that this confirmed Ewing's view.

Both schools thus advised prophylactic excision of lymph nodes (more or less radically), Crile favouring an *en bloc* excision with the primary growth, as he believed the cancer spread by permeation, and Butlin and Spencer and others favouring excision at a separate operation, as they believed the cancer spread by embolism. It must be recalled that there were only fifteen cases of carcinoma of the larynx and one of carcinoma of the pharynx in Crile's 132 cases, and that his *en bloc* theory was not applied to these cases due to the technical inadequacies of his period.

In spite of this authoritative advocacy, there was no general enthusiasm for prophylactic neck dissection or *en bloc* excision during the next forty years. Most surgeons dealing with upper respiratory tract squamous carcinoma attacked the lymphatics only if the nodes were demonstrably involved, and then only if they believed the primary source of the cancer to be eradicated or controlled. As recently as 1957, Hayes Martin wrote: "In brief, the hundreds of cases of permanent cure following discontinuous and separate surgical removal of the primary lesions and regional lymph node metastases prove conclusively that metastasis of carcinoma is by tumour emboli which pass quickly through the lymphatic channels to be caught and arrested by regional lymph nodes, the intervening channels remaining free of disease." He states that by metastases he means palpable ones, and only when these are present does he combine the operations in an *en bloc* excision.

Modern views.—Finally, I decided to examine again the validity of the assumption that breast cancer spreads by permeation to the lymphatic nodes, and that the radical breast amputation which is based on this should be the model for the treatment of laryngeal and pharyngeal growths. Illingworth and Dick (1949) taught that permeation was the last stage in spread, after the regional nodes had already filled with embolic growth. Modern writers on breast cancer, Horn (1955), Haagensen (1956) and Handley (1957),

concur with this view. Moreover, discussing the subject more generally, Willis (1952) stated unequivocally that the spread of cancer in the lymphatic system is in the first instance embolic. The modern treatment of cancer of the breast is therefore altering in character, and many surgeons no longer perform radical amputations, while others have considerably modified their method of dealing with the axillary nodes. In other words, the analogy can no longer be made, and anyone who advocates removing laryngopharyngeal cancer together with a clinically uninvolved lymphatic area must eschew analogy and prove his point.

Treatment

I have been unable to complete an analysis of my personal cases, 52 cancers of the pharynx, and 98 cancers of the larynx, and in any case I am not at all sure how much the "nicely calculated less or more" would prove. We are after all primarily dealing with individual human beings and not with percentage differences. Nowadays I nearly always advise radiotherapy in the first instance, even with postcricoid growths, being fortunate in having available the resources of the Marsden Hospital and Dr. Lederman's skill. However, somewhat similar facilities are available to everybody in this country, perhaps not on his own door-step, but even in this automobile age travel is still not impossible. It could be said that just as surgeons vary in judgment and technical ability, so do radiotherapists and their machines. I think this criticism can be disregarded, at any rate as far as Britain is concerned, as there is a noticeable general levelling in technical efficiency in both branches, due to improvements in the interchange of information. One aspect of radiotherapy is vital—each stage of the treatment must be closely watched and estimated. In fact, the six weeks or so of treatment is virtually an extended surgical operation, every step of which must be carefully executed. Furthermore, collaboration with the radiotherapist is essential, with a mutual knowledge of what can or cannot be achieved by radiotherapy or surgery, which I now regard as complementary rather than mutually exclusive methods of treatment. After treatment is completed the patient must be examined very frequently during the first year or so, and quite frequently thereafter by the surgeon and radiotherapist responsible for the initial treatment. A careful and very tightly organized follow-up system is therefore essential, as already stressed by Mr. Munro Black. Thus surgical intervention, when necessary, can be immediate, and decided at a very early stage, sometimes even during the actual course of radiotherapy. As Mr. Shaw has indicated, the cases chiefly requiring it are the pharyngeal cancers, and the supraglottic larynx cancers. I am not convinced that irradiation followed by surgery has led to disasters avoidable by an initial operation of whatever calibre.

If radiotherapy fails to control the primary tumour, and if there are still no demonstrable metastases in the nodes, I excise the primary tumour, as radically as possible, and I only combine this with a dissection of the neck nodes if any are palpable, or discovered at operation on the primary site. But individual cases may differ widely. I am often in no doubt than an *en bloc* excision is logical and necessary, but there are other cases where I am in very great doubt, and yet others where I have no doubt at all that it is cruel and useless. Nevertheless, I do agree with Mr. Shaw that there are rare cases where an extensive surgical excision could be justified as an attempt to relieve the miseries of an uncontrolled neck or laryngopharyngeal growth (Ellis, 1958). Having decided on an *en bloc* excision, the neck really must be dissected. I can see no value in compromise or partial neck dissections, and I follow the classical beliefs in advocating and practising the complete removal of all the tissues between the clavicle and base of skull, in the plane superficial to the scalene muscles (Ellis, 1957). Mr. Shaw has pointed out that modern radiotherapy techniques only to a slight extent increase the operation difficulties, although they still somewhat increase post-operative morbidity. The operation is extensive and radical, and in my opinion it is a disabling one. The neck itself becomes a mass of fibrous tissue from the combined effects of the irradiation and the operation, and remains stiff, sometimes painful and always uncomfortable to a high degree, often for years. The loss of the sternomastoid, omohyoid, digastric and stylohyoid muscles further weakens neck movements, and the denervation of the trapezius muscle, sometimes its partial excision, weakens the shoulder. The deprivation of the larynx with the suprahyoid and infrahyoid muscles, and the presence perhaps of a somewhat inadequate pharynx are additional handicaps, to say nothing of not infrequent post-operative morbidity and the need for reconstruction operations. Nevertheless, all these disabilities must be weighed against death, and may often provide a reasonable alternative.

Improvements in anæsthesia and in the avoidance and treatment of shock, together with methods of controlling sepsis, give surgeons no divine right to demonstrate how much can be achieved on any given patient in any more or less unlimited period of time. I remain unconvinced of the value nowadays of a primarily surgical approach to these laryngopharyngeal growths, or of prophylactic neck dissection. Although I

disagree with Mr. Shaw on many counts I freely admit that he has a case, if he is prepared to disregard radiotherapy and rely entirely on surgery. Fewer technical operative difficulties are then encountered, and I willingly believe the final disabilities are lessened. However, and this is the heart of the matter, irradiation can rarely afterwards be other than palliative.

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Sir Victor Negus said that he found it somewhat difficult to follow the discussion without some particular application to special conditions. The question of removal of glands depended on the type of growth and the probabilities of metastases in glands, which could only be decided by experience. He thought it was quite impossible to decide beforehand whether there were malignant deposits in lymphatic nodes since this could only be determined accurately after removal of the glands and microscopic examination. For this reason any grading of growths as being with or without metastases in lymphatic nodes was impracticable. As regards the situation of growths, nasopharyngeal neoplasms were usually treated by irradiation, and in cases of lympho-epithelioma this might control the secondary deposits, but in squamous carcinoma removal of glands was generally necessary. The palate and tonsil was a difficult region to treat surgically because of the situation and the position of lymphatics behind the mandible. One of the principles adopted was never to cut across lymphatics but to remove the primary growth with its lymphatic drainage area, and the nodes to which these lead, all in one piece.

In dealing with carcinoma of the pyriform fossa complete block dissection, including clearance of the digastric triangle, was necessary generally on one side only. With postcricoid carcinoma both sides had to be cleared, but the distribution of the growth sometimes allowed the clearance on one side to be slightly less than on the other. The teaching of Mr. Wilfrid Trotter was still alive in the speaker's mind and he thought that there were certainly cases where something less than a complete block dissection was sufficient, for instance, an intrinsic carcinoma of the larynx spread to lymphatic nodes was unusual and it was generally sufficient at operation to expose the carotid sheath and to carry out a limited clearance. Removal of three-quarters of the thyroid gland was generally called for in subglottic cases and in carcinoma of the mouth of the œsophagus spreading on to the back of the cricoid.

As regards removal of the internal jugular vein the speaker's practice was to leave the vein if complete clearance of the gland area could be carried out by stripping fascia from the vein. There was often no necessity and some disadvantage in removing it on the side first dealt with, that is the side of greater involvement by growth. Dr. Frenckner had pointed out that in about 50% of cases only one lateral sinus was patent, with consequent changes in drainage through the internal jugular vein. It did not seem essential to carry out previous injection of the vein as there was no alternative to removing it if it were infiltrated or surrounded by growth. Having preserved the vein on the side first operated on it was sometimes found that there was occlusion on the opposite side. Sir Victor did not carry out removal of both internal jugular veins at the same time and would leave a three-week interval, but with the principles already mentioned bilateral excision had not been found necessary.

Professor F. C. Ormerod said that the subject of dissection of the neck for metastatic cancer was a very wide one and could not be discussed as a single manœuvre. He recalled the words of Dr. William Harris of New York some years ago at the International Congress of Radiology, when he said that there was as little value in talking about cancer of the larynx as of cancer of the pelvis. The larynx was a complex structure of many parts, the behaviour of cancer varied accordingly to the part in which it had origin, and required varying consideration accordingly. Members would have noted that in Mr. Shaw's list of sites of origin of cancer for which dissection of the neck had been carried out there was no mention of cancer of the vocal cord. It had been stated that metastases occur in 4% of cases of vocal cord cancer, in 14% in subglottic cancer

and in 40% of supraglottic cancer. He felt that this was probably an under-estimate but it indicated the relative frequency of metastases.

In this discussion radiotherapy really had no place but it was impossible to leave it unmentioned. In early cases of cord cancer radiotherapy was adequate and cured 85–90% of patients. The question of lymph nodes hardly arose in such cases but the field of irradiation included the danger areas. In the more advanced cases and those in which radiotherapy had failed a laryngectomy was sufficient, and unless the tumour had spread to the sub- or suprà-glottic region, dissection of the neck was unnecessary.

In subglottic cases there were very few that responded to radiotherapy—probably because of the very close proximity of the cricoid cartilage and partly due to the early metastatic spread to the inferior deep cervical nodes and to the paratracheal nodes. In such patients laryngectomy with dissection of the neck was necessary with particular care along the side of the trachea.

In supraglottic cases it is possible to treat the early ones by radiotherapy and, as the lymph drainage area comes within the field of irradiation, it is likely that if the primary lesion is destroyed by radiotherapy so also will be the malignant cells in the lymph vessels and nodes. If, however, the lesion is more advanced and there is immobility of the affected half of the larynx or there are already palpable lymph nodes, or where radiotherapy has failed, then laryngectomy with a dissection of the neck is necessary.

To wait until there are palpable lymph nodes in the neck is to leave it till it is too late as by the time one group of nodes is palpable from outside there are almost certainly cancer cells in the next group of lymph nodes, possibly beyond the scope even of a radical dissection. Whether the permeation theory or the embolic theory of spread through the lymph system is accepted does not affect the issue as in either case it is not possible to gauge how far the cancer cells have spread. The only reasonable treatment is to carry out a dissection which will as far as possible remove all infected lymph vessels and nodes. Whether this is called elective or prophylactic again does not really matter as long as the dissection is wide enough and is carried out early enough. It is essential that the larynx and all the tissues of the neck be removed in one mass and at one time. Again whether the permeation or the embolic theory is accepted there is great danger in cutting across lymph vessels which are carrying cancer cells as at any moment these cells may be extruded from the vessel into the neck tissues and give rise to a widespread dissemination of malignant disease in the neck.

Even advanced carcinoma of the pyriform fossa gives consistently good results by laryngectomy, partial pharyngectomy and dissection of the neck. It was felt for a time that in postcricoid cancer dissemination to lymph nodes was rare, but with the increased survival rate following drastic surgery cervical lymph node metastases began to appear and led to bilateral dissection being carried out. This has successfully prevented the occurrence of cervical metastases but leaves the problem of how to prevent mediastinal metastasis still unsolved.

Mr. John McFarland said that reference had been made to central clinics, to deal with major surgery of the neck. He was in favour of such clinics, centred if possible on a teaching unit, rather than having the work scattered about the region. Such a clinic found favour amongst patients; the work was of a higher quality, and it had an attraction for postgraduate students. Further, he was interested and encouraged to hear that operations on the neck might take place fairly soon after X-ray therapy had been completed. Recently he operated on a case of carcinoma of the larynx two months after X-ray therapy. The skin broke down completely and there was a wide gap in the anterior pharyngeal wall. His colleagues from the radiological department thought that he had operated too soon.

Mr. F. C. W. Capps said that in the opening papers and subsequent discussion almost every point of view had been ably put and, picking the best from each, the meeting might well come to a balanced procedure.

He was in agreement with those who advocated a generous trial for radiotherapy before major surgery, but if this was to be a safe approach much must depend on first-class therapy and cordial collaboration between surgeon and therapist. At his hospital this had always been so and their joint consultations on line of treatment and follow-up often led to a refusal by the radiotherapists to take on some cases in which they felt convinced that surgery would be better and inevitable.

The fact that one speaker had had difficulty in operating, when therapy had failed, owing to severe skin damage suggested that something was wrong somewhere.

He could not agree that recurrence after radical surgery was always resistant to radiotherapy. He had recently had two cases of laryngectomy with double block dissection in which recurrence at the lingual margin of the pharynx had responded well. Possibly these mucosal recurrences were more favourable than those in the scar tissue of the block dissection.

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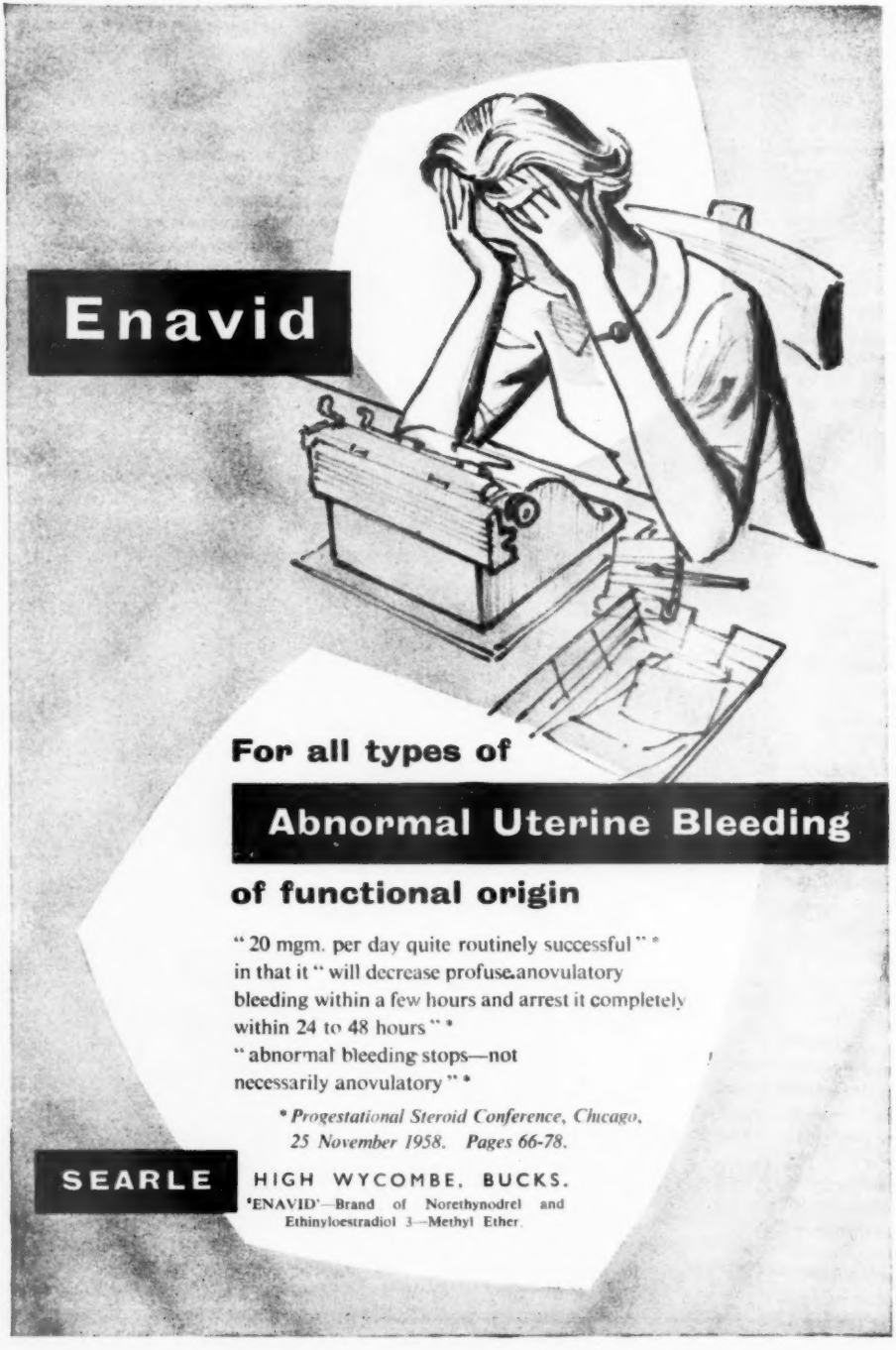
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Proceedings of the Royal Society of Medicine

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President—J. R. WHEELER, F.R.C.S.

Meeting
March 12, 1959

DISCUSSION ON LOW-TENSION GLAUCOMA

Mr. E. S. Perkins (London):

The simplest definition of low-tension glaucoma is a condition in which occur changes in the visual field typical of glaucoma, with pathological cupping of the disc but with a normal ocular tension. This definition immediately leads to the question of what is a normal tension.

The purely instrumental errors of the Schiötz type of tonometer may be considerable, and when such factors as variations in corneal thickness, corneal radius and scleral rigidity are added it is clear that the possible errors are great. Unfortunately it has usually been the habit of ophthalmologists to convert the scale reading of the tonometer into mm.Hg by using a calibration chart, and this calibration has been changed several times over the last ten years. It is particularly difficult therefore to compare values quoted in the older literature with the values we obtain to-day, even ignoring the fact that the tonometers used were not standardized.

I have long felt that we should insist on all readings being recorded as scale divisions with the weight used. Once the tonometer has been standardized the scale readings should always be the same and the very complex problem of the relation between scale reading and initial intra-ocular pressure can be left to be disputed by those so inclined. From the practical point of view a record of the weight and scale reading will always enable valid comparisons to be made on the same eye regardless of changes in the calibration scales.

The reported series of Schiötz readings on normal eyes show wide ranges of tension. Müller (1931) considered the normal range to be from 12 to 35 mm.Hg, and Jackson (1955) found a range of 10 to 40 mm.Hg. These ranges seem remarkably wide for biological variations in a physiological value and I suspect that the normal intra-ocular pressure has a much narrower range under resting conditions. The wider range obtained by tonometry almost certainly reflects the numerous errors involved in this method.

The mean values obtained by aplanation tonometry tend to be lower and the range of values smaller. Goldmann (1954) found the mean pressure to be 15·7 mm.Hg with a standard deviation of 2·9 mm.Hg. This means that 95% of the normal values fell between 9·9 and 23·5 mm.Hg. Weekers *et al.* (1959), also using the aplanation tonometer of Goldmann, found a mean value of 16·3 mm.Hg with a standard deviation of 2·5 mm.Hg. Using a standard Schiötz tonometer and the 1955 calibration scale he found a mean value of 17·07 mm.Hg with extreme values of 10 and 24 mm.Hg. Maurice (1958) using a very accurate recording tonometer has found the mean normal resting pressure to be 19 mm.Hg with extreme values of 15 and 26 mm.Hg.

Recently Becker (1958) has suggested that a scale reading of 4 or less with the 5·5 gram weight is probably higher than normal. This represents a pressure of 20·5 mm.Hg on the 1957 scale.

We clearly cannot be too dogmatic in deciding what is a normal pressure from tonometric readings, but for the purpose of an analysis into the incidence of low-tension glaucoma I have chosen a figure of 28 mm.Hg on the 1955 scale (i.e. a scale reading of 2·25/5·5 grams weight) as the upper limit of normal. Using this criterion only 58 cases (103 eyes) of low-tension glaucoma were diagnosed out of 1,700 patients referred to the Glaucoma Clinic at the Institute of Ophthalmology. This is 3·4% of the total, and corresponds fairly well with other published figures for the incidence of low-tension glaucoma. Hofe (1929) found 4 cases (1·78%) out of 223 cases of glaucoma, Nordmann and Gerhard (1957) found 8 (4·3%) out of 185 cases, and Blazar and Scheie (1950) 4 (2·6%) out of 150. These authors were able to show (by provocative tests, &c.) that some of the cases were really cases of chronic simple glaucoma so that the incidence of low-tension glaucoma is certainly not more than 2 or 3% of all glaucoma cases.

Mr. Winstanley will give more details of the 53 cases from the Institute, but some general remarks about this group may be of interest here. Most of them were in the 60–70 age group and there were twice as many female as male patients. One of the most interesting findings is the distribution of refractive errors. Of the 103 eyes 36% were myopic (9·7% more than −4·00 D), 34% emmetropic and 30% hypermetropic. The preponderance of myopic eyes is of particular interest as such eyes tend to have a larger radius of curvature of the cornea and a lower scleral rigidity than emmetropic eyes and both these

factors tend to give falsely low tonometric readings. This was borne out by the tension readings—the mean tension was highest (22·2 mm.Hg, scale reading 3·5/5·5 grams weight) in the hypermetropic eyes, and became progressively lower through the emmetropes and low myopes to the high myopes in which the mean tension was 18·9 mm.Hg (scale reading 4·5/5·5 grams weight).

Von Graefe (1857) was the first authority to describe "amaurosis with cupping of the optic disc" without increased intra-ocular pressure, although he was later persuaded that these cases were probably true glaucoma but that the rise in intra-ocular pressure was intermittent or difficult to demonstrate. Since this time many papers have appeared and several theories have been advanced to explain these cases.

I shall not give a full review of the literature but shall briefly describe some of these theories. First of all optic atrophy and field changes similar to glaucoma may follow space-occupying lesions in the pituitary region. Cases of intracranial tumour simulating low tension glaucoma have been reported by Dalsgaard-Nielsen (1937) and Blazar and Scheie (1950), and Forni (1951) reported a case of Paget's disease with similar ocular findings. De Wecker (1896) very pertinently remarks that optic atrophy in a patient with marked physiological cupping of the disc will inevitably give an appearance of glaucomatous cupping.

Congenital holes at the optic disc may also be associated with field defects and the disc appearance may give rise to suspicion of glaucoma. Neame (1947) reported 10 cases, 4 of which had field defects; Smith (1953) also described a case with a quadrantic field defect. I reported a case in 1955 (Perkins, 1955) in which a well-marked cup was associated with a ring scotoma and some peripheral constriction of the fields. Undoubtedly a few cases of apparent low-tension glaucoma will fall into the category of congenital lesions of the optic nerve, but the progressive field defects of many of the cases seen demand some other explanation.

Schnabel in 1885 introduced the concept that the cupping of the disc in glaucoma was not due to the increased tension but to a particular type of atrophy which bears his name. Unfortunately such a diagnosis can only be confirmed histologically and as Wolff (1947) pointed out, Schnabel's cavernous atrophy is only an expression of the effect on the optic nerve of a progressive diminution in the blood supply, which may be due to many causes. He suggested, however, that the formation of cavities in the region of the lamina cribrosa may help to weaken it so that it gives way under the normal intra-ocular pressure, thus producing cupping in the absence of raised pressure.

Knapp in 1932 described 10 cases with optic atrophy and cupping but with normal or only slightly increased ocular tension, in which calcification of the internal carotid arteries was seen on X-ray examination. He suggested that the atrophy followed compression of the optic nerve by the calcified vessels. McLean and Ray (1947) reported such a case in which calcification of the carotids and flattening of the optic nerves was found at operation.

However, Knapp later (1940) published a follow-up report on his original cases from which it appears that some of the patients developed a definitely raised tension although in others the tension remained normal in spite of an increasing field loss. He also found that 50% of people over the age of 60 had some degree of calcification of the carotids and suggested that an arteriosclerosis of the nutrient vessels of the optic nerve was an additional factor. Other authors (Berkson, 1951; Blazar and Scheie, 1950; Nordmann and Gerhard, 1957) have also described cases with calcification of the carotids, but it seems more likely that the calcification is only evidence of vascular sclerosis (Etzikson, 1952) and not usually the direct causative factor.

Sclerosis of the vessels supplying the optic nerve as a cause for low-tension glaucoma has had many champions (Meyer, 1950; Werner and Macdougald, 1951; Etzikson, 1952; Vail, 1953; Comberg, 1954; Rougier, 1954; and many others). Lyle recently (1957) addressed this Society on arteriosclerotic optic atrophy, which he said should replace such terms as pseudo-glaucoma, soft- and low-tension glaucoma. The visual loss in this condition may be accompanied by mental and other cerebral changes. The vascular changes start in the chiasm and optic nerves causing a degeneration which gradually extends in both directions in a type of cavernous atrophy. The field defect is often an altitudinal hemianopia. He considers that the cupping of the optic disc is probably the result of (1) atrophy and shrinking of axons, (2) compensatory and pathological attenuation of blood vessels, (3) recession of weakened lamina from the normal intra-ocular pressure. Lyle therefore looks upon this condition as quite distinct from glaucoma, although of course admitting that glaucoma should be considered in the differential diagnosis.

Sjögren (1946) on the basis of a critical survey of the literature and his own observations came to the opposite conclusion that glaucoma simplex and glaucoma without hypertension are one and the same disease, and that the latter should be considered as a symptom, localized in the eye

and optic nerve, of a circulatory disturbance of the same kind as that which, when localized in the brain, produces cerebral atrophy. The latter assertion is based on the finding of cerebral atrophy by encephalography in 4 cases.

The main evidence that Sjögren puts forward in support of his thesis that low-tension glaucoma or pseudoglaucoma is the same disease as glaucoma can be summarized as follows:

(1) Pseudoglaucoma may develop into glaucoma simplex and *vice versa*.
(2) Pseudoglaucoma can exist in one eye while the other suffers from glaucoma.
(3) Pseudoglaucoma can occasionally display an increased intra-ocular pressure, or a rise of pressure after provocation.
(4) After operation glaucoma can progress as a pseudoglaucoma.

In other words all combinations with and transitions to glaucoma may occur, and it is therefore absurd to draw a dividing line at say 30 mm.Hg, thereby creating two separate diseases—glaucoma and pseudoglaucoma.

This is a very attractive hypothesis and similar views have been put forward by many other authors (e.g. Weekers, 1942, 1943). It implies that a single pathological process may cause on the one hand a raised intra-ocular pressure with secondary effects on the optic nerve, or optic atrophy and cupping without a raised tension, or a combination of both processes, depending on which particular anatomical site suffers most severely.

If we accept this hypothesis then certain logical deductions follow. First the treatment of low-tension glaucoma by reduction of the intra-ocular pressure either by surgical or medical means should have little effect on the progress of the disease. It is apparent from the literature that many cases continue to progress in spite of a lowering of intra-ocular pressure by effective surgery, and the general impression is that hypotensive treatment is unsatisfactory. If true this does not necessarily prove Sjögren's point but only shows that the cupping and atrophy in these cases is not secondary to a raised intra-ocular pressure.

If, however, in simple glaucoma the degenerative process is causing both the raised tension and the optic atrophy, hypotensive treatment will not affect the process in the optic nerve and the field defects should progress in spite of the reduction of intra-ocular pressure. Even if it is postulated that the raised pressure is an additional embarrassment to the circulation at the disc, further progression of the field changes would be expected although at a slower rate. It is hard to believe that the widely accepted hypotensive treatment of glaucoma does not influence the progress of the field changes in the majority of cases, otherwise such forms of treatment would have been discarded long ago. There have not, however, been many critical analyses of the long-term results of such therapy.

The question was discussed recently at the XVIII International Congress of Ophthalmology in Brussels, and Weekers (1958) reported the results of an investigation into the relationship between ocular hypertension and the perimetric changes in open angle glaucoma. He concluded that the field changes are nearly always arrested when the ocular tension is kept below 17 mm.Hg, but that there is a considerable variation in the individual sensitivity of glaucomatous eyes to dysregulation of ocular tension, possibly resulting from individual variations in the anatomy of the circulatory network at the head of the optic nerve. In the same symposium I presented some data on the progress of field changes in patients with open angle glaucoma whose tension had been controlled below 28 mm.Hg by medical or surgical means. The series comprised 43 eyes with a mean follow-up period of 2·34 years, and of these 5 (i.e. 11·6% of the eyes) showed some deterioration in the visual field over this period. The vast majority, however, showed no deterioration over this admittedly rather short observation period.

It seems therefore that in most patients with open angle glaucoma the field defects are clearly related to the raised pressure, although in a small number the changes may progress in spite of a normal pressure. If therefore Sjögren's hypothesis is correct that simple glaucoma and pseudoglaucoma are one and the same disease we must postulate that the vascular changes responsible for the raised tension are found very much more commonly than those occurring in the optic nerve. It may of course be argued that the pathological changes in the optic nerve are not enough in themselves to cause functional defects and that the latter only become manifest when the tension is raised. Harrington (1958) has investigated the relation between the visual field defects in open angle glaucoma and the rate of blood flow in the optic nerve and considers that those patients with glaucoma who exhibit the most extensive and rapid field loss are the ones with generalized arteriosclerosis, low systemic and retinal arterial blood pressure. Conversely, a relatively slow rate of visual field loss can sometimes be predicted in an individual with increased intra-ocular pressure if the systemic andespecially the retinal blood pressure is elevated and there are minimal arteriosclerotic changes in the retinal arterioles. Such a correlation is exemplified by the rapidly progressive field loss occurring in cases of glaucoma in which the intra-ocular

pressure is static or even well controlled by miotics but in whom the systemic blood pressure is reduced by administration of one of the derivatives of *Rauwolfia serpentina*. Bailliart (1933) has also emphasized the importance of the retinal arterial pressure. In this connection it would be most interesting to know whether patients with carotid occlusion on one side and with a low retinal pressure ever develop field changes in the presence of a normal intra-ocular pressure.

The participation of cerebral atrophy in glaucoma as suggested by Sjögren seems to me to require considerably more evidence before it can be accepted. It must be demonstrated that such changes occur in a higher proportion of patients with glaucoma than in those with degenerative vascular disease without glaucoma, before the point is proved.

There is one vascular condition leading to obliteration of the branches of the ophthalmic artery which might be expected to produce the signs and symptoms of pseudoglaucoma, and that is temporal arteritis. As far as I know, however, temporal arteritis does not produce this picture.

Finally I should like to discuss the concept that low-tension glaucoma is only an early stage in open angle glaucoma or differs from ordinary glaucoma only by virtue of the fact that the eye concerned has a tension which, although lying in the range of normal tensions, is actually raised for that particular eye. There are two possibilities here; either the tension as measured by the tonometer does not reflect accurately the intra-ocular pressure because the eye concerned has an abnormal scleral rigidity or some other condition leading to an underestimation of the pressure, or the pressure is in fact within the normal range for most eyes but is really elevated from a previous level in the low normal range. If, for example, we find a tension of 22 mm.Hg, is it possible that the true normal pressure for this eye is only 12 mm.Hg? If so, this eye may have a pathologically raised pressure although the actual value is within the normal range.

Following the work of Leydhecker (1956), Becker (Becker and Christensen, 1956; Hildreth and Becker, 1957) has suggested that the most reliable guide to the diagnosis of early open angle glaucoma is a combination of the ocular tension and the outflow resistance as measured by tonography. In a comparison of a large series of glaucoma cases and normals he found that the ratio of tension divided by the coefficient of outflow (P_o/C) was 100 or more in 71% of the glaucomatous eyes and only 2% of the normal eyes. The proportion of glaucomatous eyes with a P_o/C of 100 or more rose to 97% after the ingestion of 1 litre of water whereas only 1% of the normal controls reached this level.

The validity of these results will have to be confirmed by other workers before they receive general acceptance but it is clearly logical to relate the tension and outflow resistance by some such method. What such a ratio implies is that for any normal intra-ocular pressure there is a corresponding value for the resistance to outflow; for example an eye with an intra-ocular pressure of 20 mm.Hg should have a coefficient of outflow greater than 0·20. Conversely if an eye with a coefficient of outflow of 0·20 has an intra-ocular pressure of more than 20 mm.Hg that pressure is abnormally high for that eye. Clearly the inaccuracies of tonometry and tonography are such that in individual cases the P_o/C ratio should not be applied too strictly, but in considering groups of patients it probably allows a broad division into normal and abnormal groups.

I should like to end by posing four questions which I think summarize the main theories and which may act as a starting point for discussion:

(1) How many (if any) cases of low-tension glaucoma are due to congenital lesions of the disc or pressure on the optic nerve from space-occupying lesions or calcified carotid arteries?

(2) Is low-tension glaucoma a distinct entity unrelated to open angle glaucoma, e.g. an arteriosclerotic optic atrophy? Or

(3) Is it one extreme of a syndrome in which some vascular disease may cause a raised intra-ocular pressure or optic atrophy, or the two combined, depending on the anatomical site of the lesions? Or

(4) Is it the same disease as open angle glaucoma, either in an early stage, or occurring in an eye with a naturally low intra-ocular pressure?

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Mr. J. Winstanley (London):

As Mr. Perkins has said, the object of our studies has been an attempt to establish whether, after fuller investigation, the clinical diagnosis of low-tension glaucoma could be upheld in the cases classified as such at the Glaucoma Clinic of the Institute of Ophthalmology.

As there has never been any wide agreement as to the criteria for the diagnosis of low-tension glaucoma, it was not surprising, in reviewing these cases, to find that different observers used a variety of standards by which to classify their cases. It was therefore agreed to exclude from the main group, described by Mr. Perkins, all those patients whose maximum tension at their initial examination exceeded 28 mm.Hg.

When this had been done there remained 20 patients (39 eyes) whom it was possible to study fully.

The criteria then, by which these 20 patients were selected, were that one eye at least must show:

(1) Pathological cupping of the optic disc.
(2) A visual field defect.
(3) A maximum ocular tension, not exceeding 28 mm.Hg.

In 6 of the 20 patients these findings were unilateral, the other eye being normal.

The investigations which have been carried out in this study are:

(1) Field studies by perimetry and scotometry.
(2) Tonometry by aplanation and indentation.
(3) Tonography before and after water drinking.
(4) Provocative tests by water drinking and dark-room, and in some cases by subconjunctival Priscol.
(5) Gonioscopy.
(6) Ophthalmo-dynamometry.
(7) Radiography of skull.

I propose to discuss these findings *seriatim.*

Of the 20 patients 5 were male, 15 were female. The average age of the males was 68, females 65. The average time interval between the initial examination at the Glaucoma Clinic and this study, i.e. the duration of the follow up, is fifteen months.

With regard to the refractive state of the 39 eyes:

15 (38%) were emmetropic.
13 (33%) were hypermetropic.
11 (29%) were myopic (4 greater than 5 dioptres).

Visual field studies.—14 of the eyes showed an arcuate scotoma only, which remained stationary during the period under review. 13 showed a scotoma which had broken through to the periphery, but which remained stationary during the period under review. 6 showed progressive field loss, and 6 were normal at the initial examination and remained so.

Optic discs.—There was nothing remarkable about the appearance of the optic discs, nor of the type of cupping. It is perhaps worth mentioning that 6 of the eyes showed a marked degree of inferior conus.

Tonometry.—It had been expected that with the advent of the Goldmann aplanation tonometer a series of pressure readings would be obtained which would be considerably higher than those obtained by Schiötz indentation, and this expected difference was to be attributed to the scleral rigidity factor—a factor which may cause an abnormally low reading on Schiötz tonometry in cases where the scleral rigidity is low owing to scleral thinning or other factors. Some observers have reported that an abnormally low scleral rigidity probably accounts for many cases of apparent low-tension glaucoma. Such has not been the case, however, in the series under review. Fig. 1 shows diagrammatically the distribution of readings of the resting tension by the aplanation and indentation methods. It will be seen that while the aplanation method gives consistently higher readings, the difference is not great, only of the order of 1 mm.Hg on the average. Fig. 1 also shows that the mean tension lies well within normal limits and in fact on the low side of the normal range. Similarly Fig. 2 shows the distribution of scleral rigidity

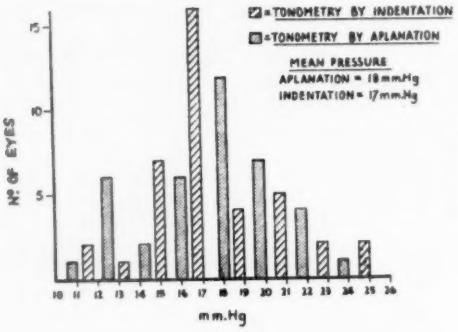

FIG. 1.

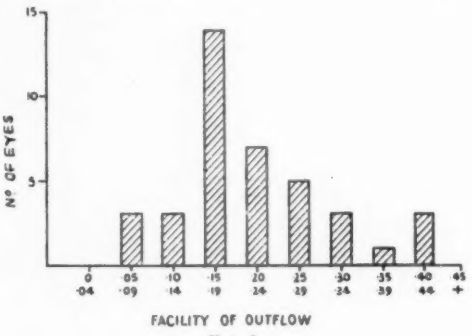

FIG. 3.

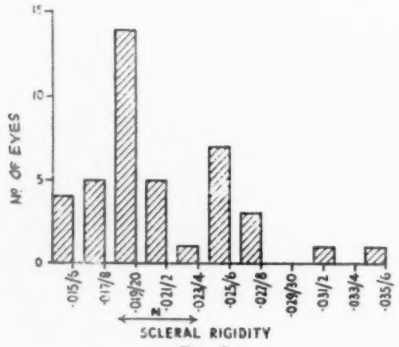

FIG. 2.

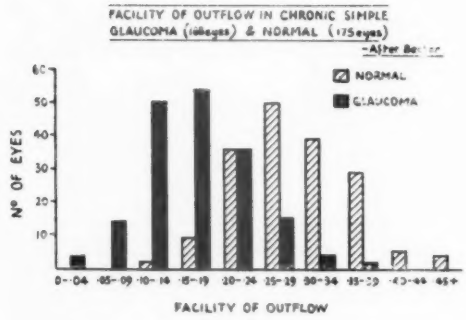

FIG. 4.

readings, and it will be seen that they are scattered fairly evenly about a peak which coincides with the normal range; such asymmetry as is present favours a higher rather than a lower scleral rigidity than normal. It does not seem, therefore, that in this series a low scleral rigidity can account for the low-tension readings.

Tonography.—Fig. 3 illustrates the distribution of readings for facility of outflow in the eyes under review—this shows nothing very remarkable except that the peak is probably below the mean of the normal range.

The main interest here has been the application of Becker's observations, with regard to tonography in borderline cases of chronic simple glaucoma. Becker has pointed out that the water drinking provocative test is positive in only 30% of cases of established chronic simple glaucoma. He has also shown that there is a wide overlap in the distribution of facility of outflow in cases of chronic simple glaucoma (CSG) and normal eyes as Fig. 4 shows.

Either of these criteria by themselves, i.e. the facility of outflow or water drinking provocation, may therefore be misleading in the assessment of

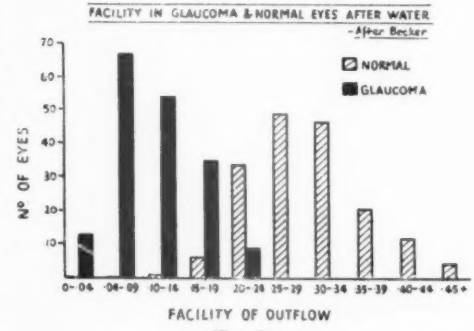

FIG. 5.

glaucoma suspects. Becker went on to show that an additional effect of water drinking on eyes with established chronic simple glaucoma was a transient reduction in the facility of outflow as measured by tonography (*see* Fig. 5) and further that this response to water drinking occurred in the great majority (82%) of eyes known to have chronic simple glaucoma.

Becker then sought a method of analysis which would tend to separate the glaucomatous from

the normal population and he used a simple function which had been devised by Leydhecker and which was called the ratio P_o/C (Table I)

TABLE I.

Ratio P_o/C where P_o = Initial tension at start of tonography
C = Facility of outflow.
Resting ratio $P_o/C > 100$ in 71% cases CSG
Provoked ratio $P_o/C > 100$ in 97% cases CSG
(After Becker)

where P_o represents the ocular tension as measured at the commencement of tonography and C the facility of outflow. It was found that if this simple ratio was worked out in a series of glaucomatous and normal subjects the ratio P_o/C was greater than 100 in 71% of the cases of glaucoma. Further, if this ratio was calculated from the results of tonography immediately following water drinking (which it will be recalled may not only raise the factor P_o but may also diminish the factor C) then the ratio P_o/C is found to be greater than 100 in 97% glaucomatous subjects but in only 1% of normals.

We therefore thought that it would be illuminating to carry out tonography along these lines in this series of patients and we have called the ratio P_o/C the provoked ratio after water drinking, as opposed to the resting ratio when measured without provocation.

In this series of 39 eyes we found the resting ratio P_o/C greater than 100 in 19 eyes, and the provoked ratio greater than 100 in a further 3, and therefore, if we accept Becker's findings, 56% of these eyes are in fact glaucomatous, a conclusion which one would certainly not have reached by a consideration of either the figures for facility of outflow or ocular tension alone.

Provocative tests.—Dark-room: In one patient of the series (both eyes), in spite of being found to have open angles of medium width on gonioscopy, the ocular tension rose 8 and 11 mm.Hg respectively, and so he has been classified as a subacute close angle glaucoma.

Water drinking: One patient had a rise of 10 mm.Hg in both eyes half an hour after water drinking and has therefore been classified as glaucomatous.

Priscol provocation: This test was carried out on patients whose response had been negative to other provocative tests and in one patient (both eyes) the response was positive.

Ophthalmodynamometry was carried out on those patients in whom the diagnosis of low-tension glaucoma seemed the most tenable. It was felt that this investigation would reveal any abnormality in the arterial pressure of the carotid system which might be expected to be present in a state of relative glaucoma due to a low ophthalmic-arteriolar pressure. This investigation, however, revealed no such abnormalities.

Radiography of skull.—This investigation was carried out in order to reveal any evidence of calcification of carotid arteries, or of those of the base of the brain, and to exclude any bony changes in the region of the pituitary fossa. In no case, however, were these changes found.

The findings are summarized in Table II.

TABLE II

Investigation	No. of eyes
Water drinking response > 8 mm.Hg	2
Dark room response > 8 mm.Hg ..	2
Resting factor $P_o/C > 100$	19
Provoked factor $P_o/C > 100$	3
Priscol provocation > 8 mm.Hg ..	2
Congenital pit of optic disc	1
Normal eyes	6
Low-tension glaucoma	4
Total	39

The 6 normal eyes occurred in patients whose abnormality was unilateral and it is interesting to note that in these eyes the P_o/C factor was less than 100 in all except one, and it will be especially worth following up this case in order to see whether this eye is the first of the group to show definite signs of glaucoma.

Only 4 eyes remained in which the diagnosis of low-tension glaucoma seemed to be tenable, and of these one was an only eye, 2 were paired and the fellow of the last eye was normal. There appeared to be nothing remarkable about any of these patients, nor any common factor shared by them all.

It remains to be seen whether it is justifiable to accept the following criteria for the diagnosis of chronic simple glaucoma:

(1) Pathological cupping of the disc.
(2) Visual field defect.
(3) A provoked P_o/C ratio greater than 100.

If this proves to be correct, and only prolonged follow up will provide the answer, then in only a few cases will it be justifiable to separate low tension glaucoma from chronic simple glaucoma.

Finally, I should like to acknowledge the technical help of Miss Kent-Norris of the Institute of Ophthalmology.

Mr. J. Primrose pointed out that cupping was delayed for many years in some eyes in spite of a raised tension. On the other hand he quoted a case of Mikulicz's syndrome which in 1935 developed cupping with a normal tension; the progressive field loss was controlled following a trephine operation in 1944 which produced a low tension (8 mm.Hg Schiötz).

Mr. O. Gayer Morgan considered that the typical clinical picture of cavernous atrophy was that of a person who is noted to have a deep physiological cup at the age of 30, and at subsequent examinations over the next two or three decades it is found that the cupping slowly increases until they may have very deep cupping at the age of 60. In spite of this no field loss can be found and it is not until even later than this that a Bjerrum scotoma slowly develops. The typical appearance is that of a generalized very excavated cupping—never localized as in chronic simple glaucoma.

Mr. F. W. Law remarked that such cases tended to show a rise in tension when the field changes developed. He also quoted a case of a woman whose tension was regularly found to be 40 mm.Hg Schiötz but who only developed field changes after twenty years.

Mr. E. F. King asked whether any of the cases in the series described had a familial incidence.

Mr. S. J. H. Miller asked whether the degree of hæmodilution following the water drinking test had been measured as it had been shown that a positive test only occurred if hæmodilution took place. He also asked if there was any tendency for the tension to increase with age.

Mr. H. Lytton pointed out that when the pressure in the eye became raised, as during tonography, the formation of aqueous humour might be diminished. This would upset the tonographic calculations.

Mr. R. C. Davenport was particularly interested to hear of the high proportion of cases with myopia and asked whether in the cases in this series the loss of field had been restricted to the central area.

Mr. F. A. Williamson-Noble asked whether the diameter of the cornea had been measured, as he had found that some of this type of case had a small corneal diameter.

The President asked how the ocular rigidity was measured.

In reply **Mr. Perkins** said that the cases described by Mr. Primrose and Mr. Law showed that there was a wide difference in the ability of individual optic discs to withstand a raised tension and that in some cases, due to other factors, the disc was unable to withstand a normal tension. He was most interested in Mr. Gayer Morgan's description of cases and suggested that perhaps these fell into the category of optic atrophy occurring in a patient with physiological cupping.

In reply to Mr. King, no familial incidence was noted in these cases but it had been described in the literature.

In reply to Mr. Miller, the degree of hæmodilution had not been measured but he agreed that this was desirable and might have accounted for the failure to provoke some of the cases. As regards the relation of tension to age, Becker (1958) had recently shown that although the mean tension of people in older age groups did not differ significantly from those in younger age groups there was a wider range of readings in the older age groups.

Mr. Lytton's point was a very important one and received support from some recent experimental work (Langham, 1958). One of the fundamental assumptions in tonography was that aqueous formation was unaffected by the application of the tonometer. If this was incorrect it would invalidate much of the tonographic work.

In reply to Mr. Davenport, it had not been noticed that the field loss in these cases tended to be confined to the central area.

In reply to Mr. Williamson-Noble, the corneal diameters had not been measured. The scleral rigidity was calculated from the aplanation and Schiötz readings on the same eye.

Summarizing the discussion, Mr. Perkins said that it was clear that cases of true low-tension glaucoma were rare and the diagnosis should only be accepted after a rigorous investigation to exclude early simple glaucoma. Even then such cases should be followed up for long periods as a manifestly raised tension may develop later. The ratio of P_o/C after water drinking may be of considerable help in the diagnosis.

When early chronic simple glaucoma cases were excluded there did remain a small group of cases whose cause was obscure. Congenital malformations of the disc and space-occupying lesions might account for occasional cases. Calcification of the carotids had not been found in any of the cases seen at the Institute and it seemed unlikely that this was a cause except in very rare cases. Arteriosclerotic optic atrophy remained as a possible entity although considering the number of people with advanced arteriosclerosis it was surprising that optic atrophy from this cause was not seen more often.

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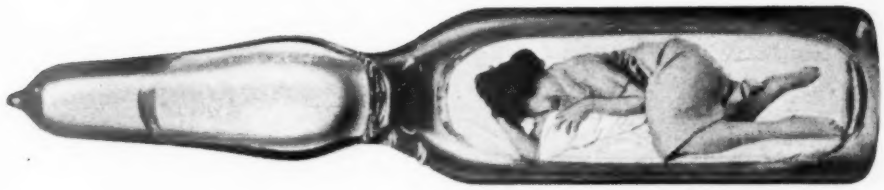

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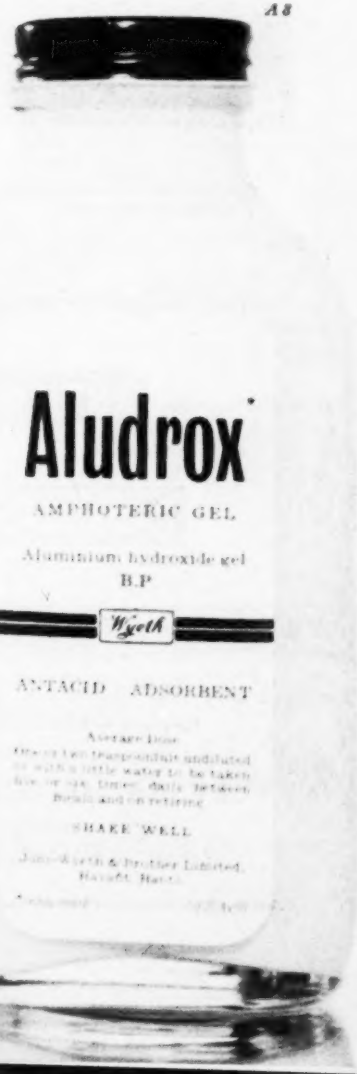

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President—A. H. Douthwaite, M.D., F.R.C.P.

Meeting
January 27, 1959

DISCUSSION ON THE IMPORTANCE OF AUTO-ANTIBODY DISEASE IN CLINICAL MEDICINE

Professor G. A. Smart (Newcastle upon Tyne):

Introduction: Renal and Thyroid Diseases

General Considerations

As Burnet (1954) has so ably emphasized, a crucial concept is that the body is able to distinguish between "self" and "not-self" so far as potentially antigenic substances are concerned. Any substance, potentially an antigen, which is present in the circulation at an early stage of development (in the human up to a short while before birth) is thereafter accepted as being "self" and evokes no antibody response. This has been shown experimentally in animals and occurs naturally very rarely in the human, as exemplified by the remarkable case described by Dunsford (1953) of a woman of 25, the survivor of a pair of binovular twins, who had cells of groups O and A in approximately equal numbers in the circulation. Potentially antigenic substances which have not been present in these early stages may evoke the production of antibody and a subsequent antigen/antibody response—this being a means used by the body to rid itself of the foreign substance.

Thus one can see several possibilities wherein body structures may come to be involved in this sort of reaction:

(1) Molecules of structures, which are normally out of contact with the circulation, may be released into it because of abnormal circumstances—for example, by trauma. A good example of this is the hypersensitivity to lens substance which may develop after intracapsular removal of cataract, when lens substance is spilled into the surrounding structures. After an interval, an intense reaction may occur in the region of the lens in the other eye. Extracapsular removal of the lens which is not associated with the escape of lens substance is not followed by such a reaction in the other eye. Sympathetic ophthalmia may also belong to this type of reaction.

It is possible that some cases of thyroid disease with associated circulating antibody to thyroglobulin may also belong to this type.

(2) A normal body constituent may be altered so that it becomes a potent antigen. This might occur either by some alteration such as denaturing (Uwazumi, 1934) or by its combination with a foreign substance which renders it antigenic (Landsteiner, 1945). The antibodies evoked might react not only with the original antigenic complex but also with the normal body constituent, though this has never been demonstrated, and this new tissue-antibody complex might in its turn stimulate the production of further antibody (Najjar and Fisher, 1955). In this way a chain reaction might be produced.

Antibodies may be free in the circulation or they may be present only in cells and the type of reaction produced by an antigen must depend to some extent upon the sort and situation of the antibody it evokes as well as upon its own characteristics.

The detection of antibodies can be carried out in a number of ways:

(1) Biologically, by observing the reaction to an injected antigen, or by other techniques such as passive transfer or the use of the Schultze-Dale preparation.

(2) By observing the precipitation which might occur when an antigen and its antibody are mixed in the right proportions. This can be studied quantitatively—a somewhat difficult technique—or qualitatively by diffusion techniques such as those developed by Ouchterlony (1949) and Oudin (1952).

(3) By causing either an antigen or an antibody to adhere to the surface of a foreign particle (often a red blood cell). In the presence of the appropriate antibody or antigen, or sometimes with some increase in the complexity of the system, the particles will agglutinate (Boyden, 1951; Boyden and Sorkin, 1955).

(4) By observing in various ways the reaction between the antibody and an anti-antibody (Coombs *et al.*, 1945).

(5) Indirectly, by mixing antigen and antibody in the presence of "complement" and then determining whether any complement has been utilized.

The presence of an active antigen/antibody reaction *in vivo* may possibly be inferred if the circulating complement level is low or by detecting the presence of antibodies to complement adsorbed on an antigen/antibody complex—so-called immunoconglutinins (Marks and Coombs, 1957).

Renal Diseases

The evidence that auto-immunity plays a part in several renal disorders is indirect, but it is nevertheless very suggestive.

Acute diffuse glomerulonephritis (Type I, Ellis, 1942) is known to occur in epidemics as well as sporadically and tends to follow an infection with Group A streptococci of Types 4 or 12 (Siegel *et al.*, 1955). Usually there is an interval of several days between the infection and the abrupt onset of renal disease. Organisms are not found in the renal lesions, and Kellett and Thomsen (1939) and others have found that complement is low in, or absent from, the serum during this acute phase. These facts all suggest that some substance is released by the streptococci which is either itself antigenic or which reacts with some glomerular capillary substance causing this to be antigenic, the interval before the onset of the disease representing the time required for antibody formation. This second possibility is suggested by the work of Glynn and Holborow (1952) in which they produced renal lesions by the injection of renal tissue which had been incubated with group A beta-hæmolytic streptococci but not by injection of renal tissue alone. On the other hand, Rich (1956) has been able to produce renal lesions comparable to those occurring in human acute glomerulonephritis merely by giving one large intravenous injection of an antigenic substance and it is possible that some of such a substance may adhere to the capillaries until sufficient antibody is produced to cause a damaging antigen/antibody reaction.

Rich (1942*a*) has also shown that prolonged hypersensitivity reactions of the anaphylactoid type can produce lesions analogous to those of polyarteritis nodosa. This disease frequently causes destructive renal lesions and there is a good deal of evidence that it is due to a hypersensitivity reaction (Rich, 1942*b*, 1945). Schönlein-Henoch purpura is also associated with renal lesions and, indeed, as suggested by Gairdner (1948) and by Bywaters *et al.* (1957) it may at times follow a streptococcal group A infection or an upper respiratory infection not associated with group A streptococci.

How does nephrosis or the nephrotic syndrome fit into this picture? There are many underlying causes of the nephrotic syndrome, but if one eliminates the obvious ones—such as amyloidosis, the Kimmelsteil-Wilson lesions associated with diabetes mellitus, and renal vein thrombosis—one is left with a series of patients about whom there have been long arguments as to the pathology. Needle biopsy of the kidney is a weapon which is rapidly helping to remove the difficulties, but certain clinical facts should be considered.

First, the response in some patients to cortisone or allied substances is an apparently complete regression of the disease. The diuresis which ensues has been well publicized, but it would seem that complete regression of proteinuria represents something much more fundamental, a point which was entirely missed in a recent leading article (*Lancet*, 1958). Secondly, it can be seen from Table I that the prognosis seems to be much more hopeful in those patients who have responded completely to ACTH than in those who have not. One can surely deduce that such responsive patients may have a completely reversible renal lesion and indeed Kark and his co-workers (Folli *et al.*, 1958) have published details of a case in which glomerular lesions, seen only by electron microscopy, reverted to normal on treatment with corticosteroids.

TABLE I.—PROGNOSIS OF "NEPHROTIC SYNDROME" IN RELATION TO INITIAL RESPONSE TO ACTH

Type of response	Alive and apparently normal	Virtually unchanged	Evidence of nitrogen retention	Death from renal failure	Total
Rendered free from proteinuria	15	3	0	0	18
Diuresis, but residual proteinuria	8	1	3	3	15
No response	0	1	2	3	6

One action of these hormones is to interfere with antigen/antibody responses and one wonders therefore whether this action is responsible for the possible effect seen in the nephrotic syndrome.

Lange *et al.* (1951) have found that complement is low during the relapses of this condition and that its concentration increases towards normal when a remission is induced by hormonal means. They also published findings of antibodies to renal substance in the circulation of sufferers but these do not appear to have been confirmed.[1]

[1]Recently Liu and McCrory (1958) claim to have demonstrated circulating kidney antibodies in the nephrotic syndrome.

Finally, although it does no more than demonstrate that an antigen/antibody reaction is a possible explanation of the nephrotic lesions, it should be pointed out that the experimental nephritis produced by nephrotoxic serum (Masugi, 1934) may contain a whole spectrum of lesions from those characteristic of a progressive nephritis to reversible glomerular changes associated with massive proteinuria. Electron microscopic studies of these lesions have been made by Reid (1956) who used small amounts of nephrotoxic serum and they seem to be very similar to the reversible changes reported by Folli *et al.* (1958). If, however, severe lesions are produced by larger doses of nephrotoxic serum the appearances are, as one would expect, quite different (Piel *et al.*, 1955).

Thyroid Disease

The place of immune reactions in thyroid disease was dramatically disclosed in 1956 when Roitt *et al.* showed by a precipitation technique that serum from patients with Hashimoto's thyroiditis contained an antibody to some constituent of human thyroid.

Independently Rose and Witebsky (1956), by injecting extracts of the animal's own thyroid gland, produced lesions in the thyroids of rabbits of similar appearances to those described in man by Hashimoto. They later showed that tanned red cells, on to which, mainly, thyroglobulin was adsorbed, were agglutinated by the sera of many patients with Hashimoto's disease.

Owen and Smart (1958) have also used a tanned red cell technique to detect antibodies to thyroid; some of the results are summarized in Table II.

The similarity between the findings in treated cases of Hashimoto's thyroiditis and those in myxœdema, taken in conjunction with the fact that the histological appearances in Hashimoto's thyroiditis are so closely paralleled by those found and described by Bastenie (1944) during the development of "spontaneous" myxœdema, would suggest that the two conditions are closely related.

It is interesting to note that the incidence of antibodies in patients who have developed myxœdema after operation for hyperthyroidism is the same as that found in idiopathic myxœdema and much higher than the overall incidence found in hyperthyroidism. This might eventually correlate with the findings of Greene (1950) that patients with hyperthyroidism, who after operation became myxœdematous, had glands with a considerable amount of lymphatic infiltration and germinal centres—appearances which, though local, were similar to the lesions occurring in Hashimoto's thyroiditis.

TABLE II.—PERCENTAGE OF PATIENTS WITH VARIOUS STRENGTHS OF CIRCULATING ANTIBODY TO THYROID

Condition	Antibodies						No. of patients
	Absent	Present					
		Weak	Moderate	Strong	Very Strong	Gross	
Normal controls	96	2	2	0	0	0	53
Simple goitre	97	3	0	0	0	0	32
Hashimoto's thyroiditis (untreated) or treated for less than one year	19	3	4	26	33	15	27
Hashimoto's thyroiditis (treated for one year or more)	27	16	30	18	6	3	33
Non-goitrous myxœdema	20	21	30	25	3	1	69
Thyrotoxicosis (all types)	67	12	13	6	2	0	64
Myxœdema developing after operation for thyrotoxicosis	20	30	20	30	0	0	10
Reciprocals of titre	0	10 to 160	320 to 5,120	10,240 to 163,840	327,680 to $5{\cdot}24 \times 10^6$	$10{\cdot}5 \times 10^6$ to 168×10^6	

Trotter *et al.* (1957) found that patients with Hashimoto's disease could have complement-fixing antibodies to thyroid tissue and that these were probably distinct from the precipitating antibodies. This work has been greatly extended by Roitt and Doniach (1958) who confirm that the antibodies are in all probability different from those which give precipitation reactions or agglutinated tanned red-cell preparations.

They find that very few patients with Hashimoto's disease or with myxœdema are entirely negative to all forms of antibody to thyroid and that 64% of patients with thyrotoxicosis were positive to at least one form of antibody. 68% of patients with subacute thyroiditis also had some sort of antibodies as

did about one-third of those with non-toxic colloid goitres and with malignant thyroids.

In the first flush of the original findings it seemed that an auto-immune process must somehow have been started which was self-perpetuating, and which gave rise to Hashimoto's disease, if it was fairly acute; a very slow smouldering process might in the end produce myxœdema. However, it now seems that the situation is a good deal more complicated. In the first place, cases have been reported in which there was an evanescent rise in antibodies after surgery or after mumps (Felix-Davies, 1958) which would suggest that the process does not automatically become self-perpetuating. Secondly, Roitt and Doniach (1958) were unsuccessful in their attempts to demonstrate the localization of labelled antibody in the glands of monkeys, nor could they alter the morphology of the thyroid by injections of positive serum from a patient with Hashimoto's thyroiditis. Moreover, such serum did not alter the appearances of human thyroid slices *in vitro*.

It would seem that thyroid abnormality of any sort is often associated with the production of antibodies, either to thyroglobulin or to some component associated with microsome fraction of thyroid cells. If this process is to be self-perpetuating and to lead to destruction of the thyroid, more is needed—perhaps the changes in the basement membrane of the acini described by Stuart and Allan (1958) are one such factor.

It would perhaps be fair to state that our knowledge of the relationship of auto-immunity to thyroid disease is now a good deal more precise than it is for renal disease. It nevertheless has to be demonstrated that auto-immunity is a cause of thyroid destruction and that the circulating auto-antibodies which have been found are not merely an accompaniment of the disease process.

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Professor E. G. L. Bywaters (London):

Antibodies in Rheumatism

In the rheumatism field, two rather antibody-like substances, the lupus erythematosus factor and the rheumatoid arthritis factor, have appeared in the last ten years, for which everyone is trying to find an antigen—two characters in search of an author. Note that I say the rheumatism field, not the collagen diseases. It is rather ironic that the antigenicity of collagen has at last been demonstrated at a time when other substances have moved to the front of the connective tissue stage (Rothbard and Watson, 1956).

Are we right or wrong in thinking of the L.E. factor and of the R.A. factor as circulating auto-antibodies? Definition of antibody is difficult since it depends on the definition of

antigen which in turn is defined as a substance which produces antibody. One cannot be precisely defined without the other.

Antibody is gamma globulin which combines with its antigen in definite proportions depending upon their relative concentrations and molecular size. There seems to be no immunological difference between different antibodies regarded as gamma globulins. The combination of antigen and antibody can be demonstrated in various ways: by complement fixation, agglutination of sensitive or sensitized particles, by precipitins including gel diffusion, by toxin enzyme antigen neutralization, protective antibodies, by histamine release (Schultz-Dale preparation or modification) or by tissue reaction as in the Prausnitz-Küstner test, by globulin fixation as revealed by the Coombs test or the Coombs consumption test or fluorescent antiglobulin sera, by the production of anaphylaxis and by a few other methods. Cellular antibodies are more difficult to demonstrate involving skin sensitization, passive transfer or tissue culture methods.

The L.E. factor deriving from the description of the L.E. cell by Hargraves *et al.* (1948) meets many of these requirements. It can be transmitted by intravenous injection of serum both in man and in the female guinea-pig (Castillo *et al.*, 1952): it moves with gamma globulin on electrophoresis (Carlson and Möllerberg, 1958), has the same sedimentation constant of 7S and like gamma globulin passes the placental barrier (Bridge and Foley, 1954; Berlyne *et al.*, 1957; Mijer and Olsen, 1958; Oudsten *et al.*, 1958; Burman and Oliver, 1958). It gives a reaction of identity with gamma globulin on an Ouchterlony plate (Deicher *et al.*, 1959) and has a half-life of the same order as that of gamma globulin. Recent work from many different laboratories, Kunkel in New York, Miescher in Basle, Hijmans in Leyden and Seligman in Paris, indicates that the L.E. factor probably consists of several related substances directed towards various nuclear components, nuclei themselves, nucleoprotein, desoxyribose nucleic acid, histone, &c.—what is more, towards D.N.A. from the whole range of life from phage to man, a very "basic" type of reaction. These factors can be demonstrated by many different methods, complement fixation, agglutination, precipitation, globulin fixation, etc. Recently Deicher and his colleagues (1959) have produced precipitating reactions with D.N.A. from various sources showing curves characteristic of antibody/antigen reaction, with zones of antibody excess, equivalence and antigen excess. Friou at Yale (1957; 1958) and my colleagues at Taplow (Holborow, Weir and Johnson, 1957), have been primarily interested in nuclear fixation, and using frozen tissue slices or white cell smears, have been able to prove that L.E. sera (with or without complement inactivation) will deposit gamma globulin on exposed nuclei: this deposited gamma globulin can then be revealed by subsequent staining with fluorescent rabbit antihuman gamma globulin. Control experiments with normal sera fail to deposit gamma globulin on the nuclei and hence the slices do not stain subsequently with the fluorescent anti-gamma globulin. The same is seen with leucocytes.

Now this serum property is not entirely specific for L.E. and my colleagues at Taplow (Weir, unpublished observations) have found positive antinuclear fixation (A.N.F.) also in 3 out of 13 cases of liver disease and 9 out of 81 rheumatoid arthritis (R.A.). There were 7 non-lupus cases positive in this test but with negative L.E. cell preparations, but only one case without A.N.F. with L.E. cells. Various other conditions were negative for both. One of these cases of R.A. was of particular interest since the patient ultimately died after thirty years of arthritis and we were able to test her serum (which had shown the L.E. cell phenomenon and the A.N.F.) against her own tissues. They stained positively and we were able to show hæmatoxylin bodies in her tissues. Why, you ask, was this not a case of L.E.: this is a question of semantics! The L.E. cell factor is also found in a variable proportion of R.A. cases and in a few other diseases, particularly liver disease, depending on the methods used and the criteria adopted. In L.E., it is often associated with various other antibody-like substances directed towards body constituents. The final proof of its antibody nature—experimental induction—has been claimed by Meischer (1957): mitochondrial fractions of human cells produced leucoagglutinins in guinea-pigs, but nucleoprotein produced antisera which reacted with human white blood cells to produce L.E. cell-like changes.

What relation then has the L.E. factor and the L.E. cell itself to the disease: is it the cause of symptoms or an epiphenomenon like the circulating antibodies formed in infectious disease? It seems probable that some at least of the specific changes are due to this "antigen/antibody" precipitate. Thus the injection of large numbers of L.E. cells has led to glomerular lesions like wire loops (German, 1958) and it is known that the wire loop material in L.E. stains with fluorescent anti-gamma globulin (Mellors *et al.*, 1957). However, we are still a long way from knowing the mechanism and even farther

from knowing why the body starts producing this particular antinuclear factor in the first place.

Now, just as the L.E. cell factor is found in R.A., so the R.A. factor is found in L.E., but it seems to be a slightly different problem. As my colleagues have pointed out (Glynn *et al.*, 1957), the Rose-Waaler factor (found in at least 70% of patients with R.A., and also in L.E.) is an antibody-*like* substance directed against *denatured* or, as the Americans say, "aggregated" gamma globulin and usually demonstrated by agglutination of sensitized red cells, or other particles. The altered gamma globulin with which R.A. factor reacts may be obtained from any of a variety of species and is improved by heating or unfolding on the surface of a particle such as a red cell.

The R.A. factor is usually demonstrated by the agglutination of sheep red blood cells coated with a subagglutinating dose of rabbit antisheep red blood cell serum, but many modifications of the original method described by Rose and his colleagues (1948) have been developed. According to the original method this factor is absent in about 30% of adult and 88% of juvenile rheumatoid arthritis, but by Ziff *et al.*'s (1956) inhibition test it is positive in most rheumatoid arthritis including Still's disease and in about 4% of other cases.

It is not quite as easy as it is with the lupus erythematosus factor to call the rheumatoid arthritis factor an antibody. While it seems to be a gamma globulin rather than a beta-globulin as at first supposed, it differs from the lupus erythematosus factor in that it is a macromolecule with a sedimentation constant of 19S, and exists in the circulation partly as such and partly as a 22S combination with protein. It may be transfused in man, according to Vaughan and Good (1958), without ill-effect and there is no evidence of more rapid removal on repeated transfusion as would occur if it were a foreign protein. It is absent in agammaglobulinæmia with apparent rheumatoid arthritis although these cases can develop delayed skin allergy, suggesting that circulating antibodies are relatively unimportant by-products of fixed tissue or cellular antibody production. The latex fixation test is less specific than the differential agglutination titre and positive results are seen in a number of other conditions with hypergammaglobulinæmia, including sarcoidosis, lupus erythematosus, kala-azar (Kunkel *et al.*, 1958), rubella arthritis (Johnson and Hall, 1958), syphilis (Peltier and Christian, 1959), and the occasional case of liver disease. The differential agglutination titre becomes progressively more positive with age in rheumatoid arthritis for no known reason (Bywaters, Carter and Scott, unpublished data). Its chief positive association is with nodule formation (Kellgren and Ball, 1959). Finally, although my colleagues at Taplow have produced antibody in the rabbit to rabbit red cells coated with heterologous gamma globulin, which is non-species specific in that it will agglutinate human red cells coated with incomplete anti-D serum, they failed to get this reaction with rabbit reactant coated on sheep cells (unpublished data). Thus the rabbit would not produce auto-antibody and we are awaiting a more rheumatoid rabbit.

Thus the rheumatoid factor shares with the L.E. factor the property of being apparently an antibody to a universal and ancient body constituent: why these should develop we do not know, but perhaps we would do better to ask ourselves, in the light of daily trauma and infection, why not? Why do we not all develop antibodies (if that is what these two things are) to nuclei and to slightly shop-soiled gamma globulin? Is it that some people lose their self-marker system on Burnet's theory, or that by a Medawar's mechanism, some do not acquire tolerance in fœtal life, or having acquired it, lose it? Alternatively we could ask (1) whether this is the production of an *abnormal* antibody to a *normal* antigen due to change in the antibody producing cells; (2) whether what is produced is a *normal* antibody to an *abnormal* antigen or to a *normal* antigen which does not normally reach the antibody apparatus, or (3) whether the normal mechanism of self-recognition has broken down. We have not yet sufficient evidence to decide between these various possibilities.

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Professor J. V. Dacie (London):

Blood Diseases

It is only within comparatively recent times that auto-immunization has been invoked as the fundamental mechanism in the pathogenesis of certain blood diseases. Although the mechanism had been hinted at by French physicians in the first decade of the century, interest in the possibility was not reawakened until Dameshek and Schwartz (1938) described cases of acute hæmolytic anæmia thought to be due to autohæmolysins, and it was not until the early 1950s that anti-platelet and anti-leucocyte antibodies were recognized in human sera.

The validity of the concept of auto-immunization depends on what one means by the term auto-antibody. If the term is used in a restricted sense to describe an antibody developed by *normal* antibody-forming cells against the subjects own *normal* blood cells acting as antigen (whether red cells, platelets or leucocytes), then one has to admit that this sequence has not yet been proved. If the concept is widened to describe the formation of apparent antibody protein by pathologically altered or pathologically stimulated antibody-forming cells, or to include antibodies formed in response to some subtle alteration in the blood cells themselves, then the concept of "auto-immunization" rests on much firmer ground. Moreover, whether or not the antibodies we can detect are auto-antibodies in the strict sense, they act as if they were, and for convenience I shall from now on refer to them as such.

Demonstration of auto-immunization.—Anti-red cell auto-antibodies are easy to demonstrate and this is best done by testing the red cells of the patient rather than his serum. If the direct antiglobulin (Coombs) test is negative, then the probability is that the patient's hæmolytic anæmia is not being brought about by auto-antibodies, but by a different mechanism. There may be exceptions to this in rare instances, but I think it is a good working rule.

Platelets and leucocytes are much more difficult to work with than are red cells; they tend to clump together unless great care is taken in handling them and, unlike red cells in acquired hæmolytic anæmia, in severe thrombocytopenia and leucopenia it is most difficult to obtain sufficient platelets or leucocytes to test, and although, for instance, various types of anti-globulin tests applied to platelets have been described (Dausset, 1956), the results of such tests are nothing like as clear-cut as with red cells. Most workers have in fact attempted to demonstrate platelet or leucocyte auto-antibodies not by making observations on the patient's platelets or leucocytes but by looking for the antibodies in the patient's plasma or serum, using normal platelets or leucocytes as test objects. By analogy with acquired hæmolytic anæmia one would only be likely to demonstrate free antibody in the most severely affected cases, at a time when so much antibody was being produced that not all of it was adsorbed by the patient's leucocytes or platelets or by their precursor cells in the bone-marrow. In mild cases tests for antibodies in the patient's serum would be unlikely to be positive.

There is another complication: platelet and leucocyte groups exist so that even when the patient's serum agglutinates the test cells it is not easy to be certain that one is dealing with an auto-antibody which would also agglutinate the patient's cells, if any were available for test, or with a group iso-antibody, analogous to the well-known anti-red-cell antibodies anti-A and anti-B. Particularly is this true if the patient has been transfused previously. In theory, it should be possible to carry out the tests with platelets or leucocytes of the same group as the patient. In practice, this is not yet feasible.

Incidence of auto-antibodies.—Auto-antibodies can be found in probably the majority of cases of acquired hæmolytic anæmia of apparently

unknown origin and in a lesser proportion of those patients who have clinically important hæmolytic anæmia grafted on to an underlying disease. But no worth-while statistics are available. In my own experience, I have seen many cases with positive antiglobulin tests and relatively few with no evidence at all of auto-antibodies. The patients are, however, a highly selected series and this I feel probably applies to other data also.

When it comes to idiopathic thrombocytopenic purpura (I.T.P.) the position is still more obscure (Dausset, 1956). In our own experience at the Postgraduate Medical School nearly all the agglutination tests we have carried out have seemed to us to have given negative results; on the other hand, a proportion as high as 75% has been found by other workers (Harrington and Arimura, 1958). It is of course possible that platelet antibodies exist most commonly in incomplete forms which cannot be demonstrated by ordinary agglutination techniques, but I should add that Coombs *et al.* (1956), using a sensitive mixed agglutination antiglobulin technique, which gave good positive results when applied to the sera of rabbits artificially immunized against human platelets, failed to obtain a single positive result when the test was applied to 34 sera from human subjects suffering from thrombocytopenia.

The relationship between leucocyte auto-antibodies and granulocytopenia is even less clear-cut and more uncertain than with platelet antibodies. It is known that leucocyte iso-antibodies exist and they are quite commonly found in the sera of patients who have had repeated transfusions and may in fact be a cause of pyrogenic transfusion reactions (Dausset, 1957). Leucocyte agglutinins have been demonstrated in the sera of patients with idiopathic leucopenia, but almost always only in patients who have been transfused, and such antibodies, when tested, usually fail to produce convincing agglutination of the subject's own leucocytes.

I think it probable that platelet auto-antibodies do exist and that so-called "idiopathic" thrombocytopenic purpura is basically, in most cases at least, an auto-antibody-induced disease. Bone-marrow studies reveal evidence of extensive damage to megakaryocytes and it is possible that the antibodies are directed against these cells rather than against the platelets which are but fragments of their cytoplasm. This may perhaps be one reason why platelet auto-antibodies are so difficult to demonstrate convincingly. The question of leucocyte auto-antibodies is still more uncertain and I have no decided views on the subject.

Hypotheses as to the mechanisms of auto-immunization.—The problem in simple terms is as follows: Why after years of tolerance of his own blood cells does an individual suddenly become intolerant of them and destroy them at a rapid rate, and even perhaps kill himself in the process?

At least four hypotheses have been put forward. None is entirely satisfactory, but it seems highly probable that acquired hæmolytic anæmia associated with auto-antibody formation is a syndrome which may result from a number of different causes. A second point to make, and this is a great handicap, is that to the best of my knowledge no one has yet satisfactorily produced an auto-antibody-induced hæmolytic anæmia experimentally in animals. What I shall say with regard to ætiology applies, I think, equally to the hæmolytic anæmias, thrombocytopenias and granulocytopenias.

The first hypothesis may be stated as follows: The red-cell surfaces are altered *in vivo* by bacterial or viral products or enzymes or by some other (as yet unknown) mechanism so that the altered cells act as antigens to which the normal antibody-forming tissue responds. The antibodies thus formed cross-react with normal red cells. This hypothesis is attractive but it is one for which I believe there is no firm positive evidence in man. It is, however, a possible explanation for certain experimental results.

The second hypothesis is that heterologous antigens lead to the formation of antibodies which cross-react with human red cells. This is probably the explanation of the presence of high-titre cold agglutinins which sometimes occur apparently as a transient response in cases of virus pneumonia. Even with this hypothesis one has to postulate in addition a peculiarity of the patient's response to the infection, for it is only in a small minority of patients that the cold agglutinins are of sufficiently high thermal amplitude to cause hæmolysis *in vivo*. Similar high-titre cold antibodies are produced in some patients continuously for years, apparently without cause. These lead to a chronic hæmolytic syndrome. If these antibodies are also of heterologous origin, then one can only say the antigen is unknown.

The third hypothesis is that a pathological change in the antibody-forming tissue leads to loss of its fœtally-acquired tolerance to normal blood-cell antigens. That is to say, the red cells are normal and the antibody-forming tissue is abnormal. This hypothesis is attractive; in its favour is the quite frequent association of auto-antibody hæmolytic anæmia with lymphatic

leukæmia and reticulosarcoma. If such disorders are brought about by, or associated with, somatic mutation then this might be expected to be associated with the loss by potentially antibody-forming cells of some or all of their normal complement of "recognition units", enabling normal body constituents to act as stimulants to antibody synthesis (Mackay *et al.*, 1957). It is also a possible hypothesis that a somewhat similar change might occur in antibody-forming cells and give rise to antibody formation, yet not be associated with overt malignancy.

The last hypothesis is one that I recently proposed (Dacie, 1958). It is purely speculative but I put it forward again in an attempt to arouse interest. Eyquem (1956) suggested that auto-immunization would occur preferentially against antigens developed relatively late in the course of fœtal development but would be more difficult against antigens appearing at the start of fœtal life. The hypothesis I put forward was stated in more specific terms. It was that some patients with acquired hæmolytic anæmia develop the disease because tolerance to Rh, or similar antigens, is not acquired, or only imperfectly acquired, in fœtal life.

It is most interesting to note that acquired hæmolytic anæmia apparently never seems to be brought about by antibodies directed against the ABO antigens. Is it possible that this is due to these antigens being more effective than Rh antigens from the point of view of impressing their particular pattern upon developing fœtal antibody-forming cells? Differences in the solubility of the antigens, time of development in fœtal life, persistence of antigen throughout the circulating life of the corpuscles, &c., might possibly explain the hypothetical difference in effectiveness. If, for any reason, tolerance to Rh antigens was in fact imperfectly acquired *in utero* in particular individuals, then the chance exposure of antibody-forming cells to autologous or heterologous Rh antigens in later life might bring about auto-immunization. I do not put forward this hypothesis with any great enthusiasm and I will not elaborate it further. There are certainly some features of the acquired hæmolytic anæmias in man which are difficult to explain on this basis, but none of the previous hypotheses seems very satisfactory either.

Treatment of Acquired Hæmolytic Anæmia and Idiopathic Thrombocytopenic Purpura (I.T.P.)

The natural history of these disorders is variable but both tend to follow the same pattern: an insidious or explosive onset, followed by gradual recovery, but with a tendency to relapse. Treatment resolves itself either in doing nothing—which is the best treatment for the patient with relatively few symptoms—or steroid therapy, blood transfusion or splenectomy.

I believe that none of these treatments affects in any way the ability of the patient to rid himself entirely of his disease. This must depend on the ultimate cause of the disorder, whether it is due to some transient circumstance not likely to recur or whether the stimulus leading to the antibody formation is long-continuing or even permanent. All that steroids appear to be able to do is to damp down the rate of antibody formation and perhaps to minimize the effects of the antigen/antibody reaction. They do this much more effectively in hæmolytic anæmia than in I.T.P., but they cannot cure either disorder, and in my opinion the doses used should be cut down to the minimum that allows, in the hæmolytic-anæmia patient, the hæmoglobin to be reasonably stable and adequate (e.g. 10 grams per 100 ml. or more). Splenectomy helps also; in acquired hæmolytic anæmia it removes an important site for the destruction of auto-antibody sensitized cells as well as perhaps a site of antibody formation. The former function appears to be the more important. In I.T.P. splenectomy again probably helps by removing an organ which filters off damaged platelets from the circulation. In I.T.P. if three weeks' treatment with relatively large doses of steroids (e.g. up to 300 mg. of cortisone) fails to produce decisive benefit the therapy should be gradually discontinued.

In neither disease is splenectomy curative; it may fail utterly in the worst affected patients. This is probably because a minor improvement in the survival of red cells or platelets in a patient making overwhelming amounts of antibody is of little or no clinical benefit to the patient. In the less severely affected patient with acquired hæmolytic anæmia splenectomy on the other hand may help considerably, for under these circumstances the spleen is likely to be of relatively greater importance in hæmolysis. Its removal may allow compensation for hæmolysis continuing at a slower rate to be effective, if not clinical cure (Chertkow and Dacie, 1956).

In acquired hæmolytic anæmia splenectomy should certainly be considered if hæmolysis continues for a matter of three months or more with no signs of improvement, particularly if the patient has to receive large doses of steroids in order to be kept in equilibrium. Transfusions should be avoided if possible, for the transfused

blood is usually destroyed by the same mechanism which destroys the patient's cells. If a patient receiving large doses of steroids still needs transfusion, the outlook is grave. Splenectomy will probably be felt to be unavoidable, but in my experience the chances of a good result are not high.

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Meeting
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DISCUSSION ON CURRENT TOPICS IN NAVAL AVIATION MEDICINE

Surgeon Captain F. W. Baskerville, Royal Navy: At the end of World War II after a long struggle the Fleet Air Arm had almost caught up with the land-based air forces in the performance of aircraft, but with the arrival of the jet we fell behind for a year or so. During the Korean episode in 1950–53 the Fleet Air Arm was operating piston-engined aircraft, namely the Firefly and the Sea Fury. These aircraft have landing speeds of 90 knots and their all up weight was between 13,000 and 16,000 lb. The Firefly had a maximum speed of 250 knots and a ceiling of 22,000 feet, while the Sea Fury was capable of 385 knots and a maximum altitude of 35,000 feet. Our largest aircraft carrier was 765 feet long and the width of the flight deck was 110 feet. In the last five years the performance of aircraft has increased rapidly and in 1959 we shall have the Sea Vixen in service in addition to the Scimitar.

These jet aircraft have landing speeds of 135 knots and an all up weight of 34,000 lb. Their maximum speed in level flight is over 600 knots and the Sea Vixen has a ceiling of 50,000 feet. The landing speed and weight of aircraft are two very important factors in landing and modern runways on land are becoming longer and can now be measured in miles. The landing speed has increased by 50% and the weight by 100%. Our largest carrier is only 808 feet long, which is an increase of only 5%, while the increase in width is also negligible. One would therefore expect that deck landing was more difficult and that the accident rate was becoming higher. This is not so, however, because of various inventions, namely:

(*a*) *The angle deck*, which came into service in 1954. It was invented by Rear-Admiral D. R. F. Campbell and consisted of extending the flight deck out on the port side, thereby making a runway clear of any aircraft parked on the for'ard end of the deck. It enables a pilot who overshoots and misses the arrestor wires to go around again instead of making him face a heavy barrier which, although usually capable of stopping his aircraft and preventing it damaging others, was the cause of much damage to his own aircraft and frequently caused injury to the pilot. This invention has improved the standard of deck landing and saved millions of pounds in aircraft.

(*b*) *Mirror landing sight*. This enables the pilot to approach the flight deck on a glide path.

(*c*) *Improved arrestor gear* which takes the load of the faster and heavier aircraft.

(*d*) *Audio air-speed indicator*. This enables the pilot to judge his speed without looking inside the cockpit at his instruments.

These factors have not only prevented an increase in the deck-landing accident rate, but they have reduced it to one-sixteenth of what it was during the years 1952–54.

What has this to do with aviation medicine? Aviation medicine is concerned with the selection and care of aircrew, the development and testing of equipment to make life possible and the training of aircrew in the use of the equipment. There is only one centre in this country capable of developing the equipment needed for high speed and high altitude flight and that is at Farnborough. This consists of the Royal Aeronautical Establishment and the Royal Air Force Institute of Aviation Medicine. The Navy is very fortunate and very proud to have a small number of officers on the staff of the Institute of Aviation Medicine. The selection, care and training of our aircrew is, however, a naval responsibility.

You may wonder why this selection is necessary, because, when you fly from Britain to America at 40,000 feet, the only selection is done by your bank manager and the air hostess is perfectly capable of looking after you. In civil aircraft the cabin is pressurized and the differential pressure between the ambient atmosphere and that inside the cabin may be as much as 10 lb. per square inch. This enables you to breathe and eat in comfort although you are well above a height which, without a pressurized cabin, would be fatal on account of anoxia.

Such a system is impossible in fighter aircraft because of the weight penalty and although these machines are pressurized to a lesser degree the aircrew fly at the equivalent of 25,000 feet for long periods and in an emergency which

causes loss of cabin pressure this may quickly change to 40,000 feet or even higher, depending on the height at which the aircraft is operating when the emergency arises. This makes it necessary not only to consider the mental and physical qualities required to fly an aircraft but also to try and detect those who are most susceptible to bends and decompression sickness at high altitudes.

Naval medical officers are also responsible for the instruction of all naval aircrew in the physiological aspects of flight and escape from aircraft and subsequent survival on land or sea. Survival at sea is naturally of the greatest importance and the water ration is one of the most difficult problems to solve. The shipwrecked mariner can expect to find at least 5 pints of water available for his use when he boards the inflatable life-raft and of course more if the raft is under-manned. The airman is not so fortunate. There is one man for each dinghy and he will be lucky if he has more than the equivalent of 4 pints of a brackish water from his de-salting kit. His dinghy is a much smaller target for the rescuers to find and he may be far from a shipping route and many miles from his estimated position.

It has been found by those who lecture aircrew on survival that the question of drinking sea water is frequently raised. There are two strongly opposed schools of thought on this subject and in order to convince themselves and their pupils that the British school was right the Air Medical School obtained permission to carry out trials. The last trial is the subject of Surgeon Lieutenant Barrington's paper.

Surgeon Lieutenant P. C. Barrington, R.N.V.R.:

Sea Water Drinking in Survival at Sea

People contemplating the horrors of survival at sea from the comfort of the shore often think that the survivor's main plight is lack of water. There is a widespread notion even in the Navy that a man will drop dead after three days without water. At sea this is of course nonsense, and it would have been better if some of the formidable rows of water kegs which accompanied Carley floats in H.M. ships until recently had been exchanged for some means of protecting the occupant from exposure, particularly cold. Very often a survivor did not live long enough to be much concerned about his water supply.

Since the advent of inflatable life-rafts the picture has changed. A survivor in one of the modern 20-man rafts should have nothing to fear from exposure, and may very well live long enough if he is not rescued to suffer from the effects of dehydration, perhaps exaggerated by seasickness.

The water supply for the 20-man raft is carried in a separate survival pack which goes into the water attached to the raft. As everything that can happen sooner or later will happen, someday the two will break apart, and a raft will be left with no water at all. Another possible situation is that of a pilot who abandons his aircraft some hundreds of miles from his carrier. He might come to the end of his two pints of de-salted water and eventually die of thirst because no one finds him. Men have saved themselves by sailing thousands of miles in lifeboats, but the man in a rubber raft must wait until help comes to him. It is for occasions like these that we must know how best to use any water that may be available, and the best thing to do if there is no water at all. If a man can last nine days rather than eight he may be rescued alive rather than dead.

One question that the survivor at sea will ask is: "Can I drink sea water?" The Naval Life-raft Handbook is quite uncompromising. It says: "It is fatal to drink sea water. Many lives were lost during the last war from this cause. Madness and death follow very quickly after drinking sea water." This view was based on work by Critchley (1943) and McCance *et al.* (1956), who analysed the depositions of survivors in the last war, some of whom had seen their companions disappear delirious over the side. The Life-raft Handbook must be completely dogmatic in order to convince the wavering survivor and maintain morale and discipline, but it must be admitted that there are two other views current:

(1) That sea water *should* be drunk in limited quantity by survivors.

(2) That sea water may be valuable if added to a fresh water ration.

The reasons for this difference of opinion after much experimental work include disagreement on the basic concepts, the large number of variable factors involved in these experiments, and uncertainty as to the meaning of the observations that have been made, particularly when they are extrapolated to describe what happens in the late stages of dehydration in man. There are three sources of information about the effects of drinking sea water: (1) Survivors' reports, (2) Animal studies, (3) Experiments in man.

(1) *Survivors' reports.*—The authors previously mentioned showed that during the last war the death-rate in lifecraft in which at least one person drank sea water was ten times that in lifecraft in which no sea water was drunk. This

is a very striking difference, but does not conclusively prove that the sea water was the cause of the deaths. It is conceivable that both the deaths and the sea-water drinking were independent results of poor discipline and morale.

(2) *Animal studies.*—If an animal can excrete urine which contains more salt per unit volume than sea water, it can theoretically live with sea water as its only fluid intake. If it drinks enough sea water it can effectively extract any quantity of fresh water from it. It is known that rats which are allowed to drink sea water live longer than rats which have no water. However, the rat kidney can excrete urine containing almost as much salt per unit volume as sea water does. Most mammals can concentrate urine more than man can, and for this and other reasons it is difficult to apply results obtained in animals to man.

(3) *Experiments in man.*—Water from the Atlantic or Pacific oceans is of salinity roughly equal to 3·5% NaCl. Body fluids are isotonic with 0·9% NaCl. The maximum concentration of NaCl which can be attained in practice by the human kidney is about 2%. Therefore if any sea water is drunk either the body fluids will increase in salt concentration, or the salt will be excreted in the urine with loss of more water than the original volume of sea water drunk.

But the situation is in fact less simple. A man drinking no water at all continues to pass 200–400 ml. urine per day under the best conditions, and this contains less than 2% salt. It has therefore been suggested that he could with advantage drink sufficient sea water to raise the salt concentration of his urine to 2%, provided that the twenty-four-hour volume of urine remains less than that of the sea water plus the obligatory daily urine. On this hypothesis the maximum useful quantity of sea water would be about 400 ml. (Ladell, 1943).

Experimental confirmation has been sought for this theory, and it has been found that of 400–500 ml. undiluted sea water given per day for four to six days, less than 100 ml. is retained each day. At the same time salt is retained, so that the final ionic concentration of the body fluids is greater than it would have been if the subject had drunk nothing. The small gain in water coupled with the large increase in body salt is taken (in this country at any rate) to indicate that 500 ml. sea water per day would eventually be harmful to a survivor.

Other experiments have been designed to show the effects of adding smaller amounts of sea water to fresh water rations. The most meticulous experiment was that of Hervey and McCance (1952). They observed the effect of adding 150 ml. sea water to a ration of 350 ml. fresh water. All the sea water was retained, but the increase in body fluid concentration on the third day was twice as great in the group drinking sea water as in the control group, when judged by Na and K balance. In an experiment in 1956 by Rubini *et al.*, measurements were made which suggest that there are great differences in the way human subjects handle a sea water load and that drinking sea water added to a fresh water ration does not necessarily cause an increase in body fluid osmotic pressure greater than if less sea water were added.

In 1957 the view taken at the Royal Naval Air Medical School was that the case against the survivor using small quantities of sea water, diluted or undiluted, was strong but not proven. A trial was therefore carried out on the Solent in a 20-man raft to obtain further information. Unfortunately this experiment coincided with the Asian influenza epidemic, which decimated the would-be survivors. Four only finished the full six days of the trial. On the basis of clinical condition and ion balance the subject who had been drinking 200 ml. fresh water and 300 ml. sea water per day appeared to be in quite as good condition at the end of the trial as the subject who had been drinking 500 ml. fresh water per day.

This result was encouraging, and a more extensive trial was planned for 1958 in which a similar ration would be tested for longer, in a larger group. This took place during the last ten days of July 1958, using 16 volunteer subjects. All members of the party were given 250 ml. fresh water daily, and 8 had in addition 250 ml. sea water. The food ration consisted of approximately 100 grams of carbohydrate per day. Ten days were available for the trial, and within that time the aim was to continue until the mental or physical state of the subjects gave cause for alarm to the medical officer in charge of the trial. It was hoped to carry on longer than previous trials to see what happened after the initial adaptation of the body had taken place.

The volunteers were an excellent group: morale was very high, and for the first five days there were few complaints. The crisis was reached on the sixth and seventh days, when there was a marked deterioration in fitness and morale. Two subjects were removed from the trial after seven days because of sleeplessness, thirst and headache. At this stage it was decided to terminate the experiment after nine complete days.

During the whole period urine was collected in

twenty-four-hour specimens for electrolyte and other estimations. This enabled the ion balance to be calculated and, using water losses estimated from the weight loss, making certain assumptions, the change in body fluid electrolyte concentration was calculated.

Results

(1) Clinical condition gave no clue at all as to which subjects were in each group. Changes in resting blood pressure and pulse were equal in the two groups. Systolic blood pressure fell by about 15%. It was expected that the sea water supplement would tend to maintain the blood volume and hence the blood pressure, by expanding the extracellular fluid space. This apparently did not occur, so we obtained no confirmation of Ladell's (1954) hypothesis that a small sea water ration would benefit a survivor during his first few days at sea by keeping the circulation in better condition than it would have been without this extra salt.

(2) Body fluid concentration rose by 4% in the control group, and 11% in the "sea water" group, as calculated by the Na+K balance method. It increased quite steadily in the two groups apart from an initial retention of ions in the sea water group.

(3) Some of the water in the sea water supplement was retained, so that the sea water group lost less body water than the control group. It is particularly interesting that the amount retained fell for the first three days and then rose again to an approximately constant figure. On the third day the sea water group actually lost more body water than the control group. In the experiment of Hervey and McCance it was noted that weight loss was less in the sea water group until the third day, when it became equal to that of the control group. This was taken as evidence of incipient osmotic diuresis. In this experiment osmotic diuresis occurred, but decreased from the third day onwards. Taking the increase in body fluid concentration and the water balance together, the effect on the body will depend on whether the disadvantage of increased body fluid concentration is greater or less than the advantage due to the water retained from the sea water ration.

(4) The plasma Na and K levels did not reflect the change in body concentration as calculated. One would expect that if Na and K were accumulating in the body as a result of drinking sea water, there would be a greater rise in plasma Na or K in the sea water group than in the control group. In fact the plasma Na rose by 3 mEq./l. in the salt water group (statistically probably significant), and by 5 mEq./l. in the control group (statistically significant). Plasma K remained practically constant in both groups, and plasma Cl, if anything, fell slightly in the control group and rose 3 mEq./l. in the sea water group. The discrepancy between the changes in calculated body fluid concentration and plasma cations has not been explained. It might mean that the balance method of calculation does not give a true indication of the change in body fluid concentration, in which case the only evidence we have adduced that the sea water supplement might be harmful would be invalid.

This experiment has not answered the survivor's question "Shall I drink sea water?" It has suggested that the case against the small sea water supplement is still not proven, by showing that increasing diuresis does not necessarily follow the ingestion of sea water, and by drawing attention to the discrepancy between the calculated increase in body fluid concentration and the measured increase in plasma electrolytes.

Until further work which will probably have to be of a more fundamental kind eventually allows us to say categorically that sea water is or is not beneficial under certain conditions, the advice in the Life-raft Handbook is right. Sea water is certainly dangerous in excess and may be dangerous in moderation: survivors should not drink it.

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Surgeon Lieutenant-Commander I. H. Colley, Royal Navy:

The effects on the body of reduced atmospheric pressure have been known for a long time, but they did not become a serious problem in aviation until the middle of the last war, as it was only then that operational altitudes rose much above 30,000 feet, the minimum height at

which *consistent* serious adverse effects of decompression are noted. In the last ten years, the successful development of the high speed jet airliner flying at an altitude around 40,000 feet has made the effects of decompression a far from insignificant problem in civil aviation as well. In the early days decompression sickness was—in the air—an academic danger; now it is an ever-present hazard associated with all flying in both the civil and military spheres.

The adverse effects of decompression are manifest in a highly individual manner, and there is no way of foretelling results in any one exposed individual. It was assumed at an early date that a certain proportion of the exposed population would be more likely to be susceptible than the rest, and so the principle of a pre-selective test was envisaged. This test had to be one of actual exposure to risk under closely supervised conditions, and was considered an essential if disaster in the air was to be avoided. It was formulated as soon as there was a naval requirement to fly at altitudes in excess of 30,000 feet.

The test consists of three one-hour runs in the decompression chamber at a simulated altitude of 37,000 feet, and at forty-eight-hour intervals. 100% oxygen is breathed throughout. To simulate actual flight conditions there is no pre-oxygenation (which would in any case invalidate the findings by producing artificial immunity). The altitude of 37,000 feet was agreed as the highest that could be used without complicating the findings with oxygen lack problems. One-hour periods of decompression were chosen so that ample time was available for symptoms to develop. By making the subjects undergo three exposures there was a reasonable chance of isolating all susceptibles. It was understood if a test were to involve say, ten one-hour runs, that whereas a more accurate forecast of susceptibility could be made, a far greater provocation of symptoms due to repeated and frequent exposures would occur, and so a test of three one-hour runs on alternate days was chosen. At the same time the Service requirement for a test of reasonable proportions was met. It was considered that a repeat of the test every four years was necessary to evaluate the greater susceptibility to decompression sickness *expected* to be found with advancing years.

Decompression sickness is a symptom complex. Bends are the most common finding, and although they are always annoying and often incapacitating, they are of little danger to life, but there is a group of far more serious and sinister findings: "Chokes" (respiratory symptoms), "Staggers" (which are technically labyrinthine, but include central nervous system symptoms as well) and "Collapse". Should these symptoms occur in the air, they will at the best make a pilot incapable of handling his aircraft safely, and at the worst result in his death. Fortunately death in the air due to decompression sickness is a rarity, but the following is an example:

In 1951, a 29-year-old engineer took off in an unpressurized aircraft and climbed steadily to only 28,000–30,000 ft. using adequate oxygen all the time. He remained at this altitude for just under one hour, and then descended and landed. As the aircraft came to rest he looked pale and felt shaky. After about half an hour he tried to vomit and said he had vague generalized abdominal discomfort. He was markedly cyanosed and admitted to hospital where he exhibited all the classical signs of severe peripheral circulatory failure. He died nine hours after landing. A full post-mortem failed to show any pre-existing pathological condition.

The classification used in the Royal Navy is as follows:

A.—Candidates who are able to remain in the chamber for the three separate one-hour runs with nothing more than skin itching, or a minor bend which does not worsen, are classified as category A and are allowed to fly at any altitude.

B.—Candidates who suffer from bends which rapidly worsen, or which require treatment by descent to ground level, are classified as category B and are not permitted to fly in an unpressurized aircraft at more than 30,000 ft.

C.—Any person who suffers from more serious symptoms in the chamber whether they be respiratory, central nervous or anything else in origin, is classified as category C and may not fly above 30,000 ft. under any conditions.

The criteria used in the categorization of the serious "C" cases, expressed in the order of the frequency of their occurrence in this series are:

(1) *Chokes.*—Where the symptoms are pulmonary in nature, with cough, tightness of the chest, dyspnœa and cyanosis. A drop in blood pressure often occurs.

(2) *Collapse.*—Where the subject is in imminent danger of collapse, or has actually collapsed, and has symptoms of shock or vaso-vagal attack with extreme pallor and cold clammy extremities, unconsciousness and amnesia for the event, also associated with a low pulse-rate and blood pressure.

(3) *Staggers.*—Where the symptoms are of cerebral origin, with palsies of one or more

limbs, loss of sensation, partial or total blindness or blurring of vision, deafness, epileptiform convulsions or unconsciousness.

(4) *A combination* of chokes, collapse and staggers in one way or another.

(5) *Post-decompression shock*.—There has been only one of these cases, but the symptoms were collapse with a marked degree of shock, low blood pressure and loss of consciousness occurring ten hours after return to ground level.

Before discussing the results of our test, it is necessary to say that when carrying it out we make every possible effort to ensure that there is no other abnormality in our subject that could account for the symptoms produced. We do all we can to exclude the slightest degree of common cold, diarrhœa or gastro-enteritis; we check that "the night before" has been a quiet one, and that adequate sleep has been taken, that the candidate does not go into the chamber without a suitable breakfast—and so on.

Results

Since this present test was instituted in 1950, and up to the end of December 1958, a total of 1,605 cases has been tested, covering an age bracket of 17–43 years, but with by far the largest number in the 19–34 group. Using the three categories A, B and C it was found that 65·2% were category A, 27·5% were category B, and 7·3% were category C.

There seems to be confirmation of the belief that there is an increase in all symptoms of decompression sickness with advancing age. In the 17–21 age group of 307 cases 76·5% were category A, 18·6% were category B and only 4·9% were category C.

By contrast, in the 29–32 age group of 200 cases, only 58·5% were category A while 34·0% were category B and 7·5% were category C.

Because of the relatively small numbers of subjects at each end of the *weight* range, it is not possible to obtain any definite confirmatory evidence from these figures to support the widely held belief that excessive weight is an aggravating factor in the ætiology of decompression sickness.

The greatest interest is focused on the serious category C cases. In this series it was found that there were 47 cases of "chokes", 30 of "collapse", 20 of "staggers", 4 of a combination of all these, and 1 case of post-decompression shock.

In addition to these 102 cases, there were 15 others graded as unfit to fly above 30,000 ft. for reasons not basically due to decompression sickness as considered here—for example those with severe abdominal distress because of complete inability to clear abdominal gases.

60 of these severe cases occurred on the first run, 23 on the second, and 19 on the third. Here is justification of the three runs employed in this complete test. Whereas by far the largest proportion of cases occur on the first exposure, if only one run had been given 42 cases or approximately 40% would have been overlooked (and thus allowed to go on exposing themselves and others to risk).

A detailed breakdown of the 142 cases retested shows that of the 106 originally category A, 71 remained so, 30 became B and 5 were made C. Of the 36 originally category B, 34 remained so, and only 2 cases were recategorized C. We do not feel justified in ever retesting a person originally category C. As yet these numbers are too small to show whether the increased susceptibility is due to advancing age alone or to some other factor. On the other hand, neither is there any evidence to show that the original test failed to pick up any large number of dangerously susceptible subjects.

Because there is a falling incidence of category "C" symptoms on each of the three runs of the test—both in the original and in the retest—it seems evident that there is indeed a certain proportion of exposed subjects more susceptible than others to the serious effects of decompression sickness, since if it were just a matter of pure chance, the incidence of category C symptoms would be expected to be the same in each run. It is thought, therefore, that this standard naval test which has remained consistent since 1950 has achieved its original object of removing susceptibles from risk.

We are agreed that the modern pressure cabin now in universal use in all military aircraft is very efficient. Even so, it can and sometimes does fail. Therefore it is necessary to-day to forecast the susceptibility of aircrew exposed for a short time to altitudes far in excess of 37,000 ft. We must go even farther, and envisage circumstances such as would occur in wartime when a strategic weapon would need to be carried. We have to ensure that should cabin pressure fail—for mechanical reasons or enemy interference—our pilot will stand a good chance of being able to complete his mission at high altitude unpressurized, and we must certainly see that he does not fail in his task because of a susceptibility that could have been foretold.

Our pre-selective testing has to be as realistic as possible, but for oxygen reasons alone it is impracticable to conduct any prolonged test at more

than 37,000 ft. There is no justification for any test at a higher altitude, even if the 37,000-ft test has been passed without symptoms; indeed, tests of this nature have resulted in fatalities. We have to accept the situation that we have gone as far as is reasonably safe in our process of pre-selection. As a result we can say with confidence that a highly susceptible subject at 37,000 ft. will be even more so at 50,000 ft. It is unfortunate that we are unable to say that a pilot immune at 37,000 ft. will remain so at 50,000 ft.

To make the test as realistic as possible in the light of modern requirements—and after categorization and training in the use of pressure breathing equipment—all subjects graded categories A and B are given practical experience of rapid decompression through a pressure differential of 160 mm.Hg. In the case of the category A subject this means a rapid decompression from 25,000 to 41,000 ft. in 2½ seconds, and in the case of the category "B" subject from 18,000 to 30,000 ft., also in 2½ seconds. These experiences are relatively realistic, and approximate to what a pilot might experience should his pressure cabin fail when he is at high altitude. After 10 seconds or so at 41,000 ft. subjects descend rapidly to 37,000 ft., and then do a normal descent to ground level.

It is believed that the High Altitude Selection Test has proved to be of value since we have had no death or incapacity or need to terminate an exercise or mission due to decompression sickness in the Royal Navy.

This may or may not be fortunate chance, but it can be claimed that the High Altitude Selection Test has played its part in this happy state of affairs. One can go so far as to question the pessimists who consider that selection offers little hope of eliminating susceptibles from risk. It seems that such a test as this—even with its obvious weaknesses and compromises—is necessary until such time as we have a guaranteed pressure cabin.

Surgeon Commander E. Boyd Martin, Royal Navy:

Psychological Breakdown in Royal Naval Flying Personnel

This paper results from an analysis of the 478 cases seen by the Royal Navy's Central Air Medical Board as cases of psychological breakdown in aviators during the period January 1, 1947, to December 31, 1958. The opinions expressed are my own and are not necessarily those of the Admiralty.

Functions of Central Air Medical Board

All the initial medical examinations of naval aviators are carried out by the Board. All cases of psychological breakdown are referred to the Board. The selection of naval aviators is a complex procedure. All candidates for pilot and observer categories are required to undergo the Royal Air Force aptitude selection procedure. Those who are successful are next medically examined. The examination has a failure rate of 20–25%. Those who pass go on to the executive selection procedure, which consists of pencil and paper psychological tests, performance in discussion, psychological interview, performance in group tasks and interview by a board of naval officers together with a civilian schoolmaster. The failure rate for this part of the total selection procedure is around 50%.

There are two variations from this. Candidates for rating (enlisted men) aircrew duties are not required to undergo the full executive selection procedure but are chosen on the recommendation of their commanding officers together with a short interview. In the case of serving officers transferring to aircrew duties it is assumed that nothing more than aptitude testing and medical examination is required.

At the other end of the scale, when an aircrew member's ability to continue flying becomes suspect on psychological grounds his case may be dealt with locally if it seems sufficiently simple to be dealt with by a period of rest or by a straightforward change of appointment. All other cases are referred to the Central Air Medical Board. The Board's function then is to decide whether the case is one which can be accepted as a medical commitment or is essentially an executive matter. Either way all these cases proceed from the Central Air Medical Board to the Naval Aircrew Advisory Board whose function is to advise the Admiralty as to their future employment. It must be admitted at the outset and, I believe, for the true understanding of the story that follows, that in general to be referred to the Central Air Medical Board, unpopularly known as the "twitch board", is viewed in the Fleet Air Arm with considerable misgiving.

Analysis of Cases Seen

It is interesting and not unimportant that it is the Central Air Medical Board that carries this slur. In fact just as the executive failure rate for candidates is twice the medical failure rate, so the executive rate for grounding aviators is twice the medical grounding rate.

Of 478 cases referred 338 or 71% were permanently grounded. 140 or 29% returned to flying duties though not all of them to full flying duties.

Of the 338 grounded 209 were grounded by executive action and 129 were medically grounded.

Expressed as a percentage of the Royal Naval flying population at risk these figures represent an average breakdown of 3% per year. The highest figure was 5% in 1948 and the lowest was 2% in 1957 and 1958. It might be argued that such a failure rate is small and acceptable. It is hoped that this paper will suggest that it is a figure that could be lowered.

The Fleet Order governing the reference to Central Air Medical Board states:

"All cases in which officers or ratings show loss of flying efficiency are to be reported to the Commanding Officer without delay. Such cases will normally be brought to the notice of Commanding Officers

(*a*) through the Squadron Commanding Officer or other Executive Officer

(*b*) through the Medical Officer

(*c*) by a personal request from the officer or rating."

In practice it works out the other way round. 71% of the cases appeared as the result of their personal request, 15% were medical "pick ups" and 14% were brought to light by the executive.

Factors Causing Breakdown

There are ten main factors causing breakdown: (1) Outstandingly first is the man's inability to throw off his past accident or accidents. There were 78 of these. (2 and 3) Equal second at 42 each were fatigue and wives' objections to flying as an occupation. (4) Temperamental unsuitability, 34 cases. (5) Out of practice, 30 cases: men who after a long time away from flying found they could not resume. (6) Inaptitude, 29 cases: men who were basically not aviators and to whom aviation had never come naturally. (7) 27 cases: those who had never had any basic motivation for flying but who had become aviators because it was their only way into the Navy, or to officer status. (8) 26 cases: an assorted collection of domestic factors, family responsibilities, finance, family health problems and (9) an equal number with an aversion from a particular type of aircraft. (10) 21 cases: those who had been beaten by the toll of their friends and acquaintances in fatal aircraft accidents.

Approximately one hundred other cases were basically due to a wider field of causes including prisoner of war experiences, dislike of a new appointment, night flying and deck landing.

Accidents.—In the Royal Navy there is always something of a battle between the executive and the doctors after any aircraft accident. Provided the aircrew are able to talk the executive wish to get ahead with their enquiries into why the accident happened. The medical officer is, or should be, just as keen to see that the person who has had the accident is rested and is not subjected to questioning by the Commander Flying, the Squadron Commanding Officer, the Air Engineer Officer and others. Unless the incident has been trivial I believe a period of sedation to be essential.

The second factor which is of importance in considering this category is indicated by my care to say "accident or accidents". One accident has been enough for some people. Others have had up to eight accidents of varying degrees of severity.

Fatigue and lack of practice.—42 cases presented primarily because of flying fatigue and 30 cases appeared primarily through being out of flying practice. It might at first seem reasonable to assume that here were two groups of people who might have done better as a whole if the one group had been rested from flying while the other had done more. In practice it does not work out so simply. The "out of practice" group is made up of people who have been away from operational flying for a matter of years—up to six or seven years—but who were in any case moving toward the end of their flying careers on the ground of age. As a whole they would not have been available as reliefs for the younger men who were working toward a state of flying fatigue.

This is very far from saying that we do not need to look very closely into the question of rest for the younger aviators. To be too long away from flying is fatal. On the other hand over 50% of the cases reviewed broke down with between 300 and 1,000 flying hours to their credit, that is the bracket within which one will find the greatest part of the Royal Naval flying population.

Wives.—The objection of wives to their husbands continuing to fly ranked equal second with fatigue as a cause of breakdown. Marriage occurs earlier in the British population than it did twenty years ago. The husband of the young wife with a growing family and growing responsibilities, the husband of the wife most likely to object to his hazardous mode of livelihood, is also going to be included in the 300 to 1,000 hours bulge. One is therefore faced with the problem that while it may be desirable to rest the husband the wife's objections may be at their strongest when the time comes for his return to aviation.

Temperamental unsuitability, inaptitude, lack of motivation.—These three factors which ranked (4), (6) and (7) are grouped together under one

heading since they may all clearly be classed as failures of selection. It has to be borne in mind that these cases do not include those who failed to learn to be a pilot or an observer.

To improve selection, I believe that the target should be raised in attracting candidates first by demanding a higher educational standard, and secondly by stressing the Royal Navy's need for the best rather than offering a suggested easy way to being a naval officer. Most of the "no motivation" group were primarily motivated by wishing to be in the Navy and not by wanting to fly.

A third factor is one which is well recognized but all too rarely acted on. It may be well to give a man the benefit of the doubt once but it is highly dangerous to keep on doing so. Too many cases are seen where it appears that from the very beginning of flying training till ultimate breakdown a man has been known to be not really up to the job.

Improving Selection Procedures

The initial medical board and the executive selection board should work more closely together. The medical board works very largely to purely physical standards. The executive board has very largely a lay psychologist's approach. I believe there to be a need for a psychiatric bridge between the two and that the Central Air Medical Board should be represented in the final deliberations of the executive board.

This statement is made with one outstanding fact in mind. When this paper was being prepared the records of the original medical examinations of those who entered aviation before 1951 were not available. As a result there was no record of the hobbies mentioned at the original examination. Where such records were available it is not without interest that over 50% had mentioned hobbies that could be described as æsthetic or solitary or both. Painting, amateur dramatics, active music, writing, rock climbing and hiking are viewed with the gravest suspicion and while they may be no reason for failing a medical examination they are certainly not factors to be ignored. In other words there is a need for the doctors to say "We do not like the general picture of this man" rather than merely to say "This man is physically fit".

One extremely interesting fact which has emerged from this analysis is the gross disproportion between the number of pilots and observers referred to the Central Air Medical Board. Of the total of 478 cases 315 were pilots, 105 were rating aircrew (enlisted men) and 58 observers. Dr. Desmond Curran, Consultant in Psychiatry, once said that to be a good fighter pilot one needed the mentality of a skiing stockbroker, to be a man who could enjoy thrills but calculate risks. 315 have failed to live up to these criteria. On the other hand only 58 observers (one-fifth as many) have been referred. Only one appeared because he lacked all confidence in his pilot. When one thinks of the general defencelessness of the observer one cannot help wondering whether his psychiatric makeup does not need to be that of a mathematically-minded rice pudding!

The great majority of these cases appear as a result of their own request. The remainder are about equally divided between those who are identified by the medical and the executive. Medically they have presented, in order of frequency, complaining of headaches, air sickness, general anxiety, vertigo, dyspepsia, insomnia. There were other presenting symptoms but they occurred in too small numbers to have significance.

Reference of Cases to Central Air Medical Board

The crux of the matter appears to be that if a man is to be rehabilitated he must be dealt with early. The fact that 73% of the cases have been seen only at their own request automatically means that they are being seen too late. A man has to reach a fairly desperate state before he will ask to be sent before the Board. I should like to see this finality of being sent to the Central Air Medical Board removed. It would be better if, in the first instance, cases were referred as for a normal specialist consultation and the Board itself decided whether the full weight of the Board procedure should be brought into action. If it decided that the full procedure was unwarranted, in other words that there was a good prospect of rehabilitation, the subject's immediate employment could be arranged directly between the Central Air Medical Board and Admiralty without the formality of the subject appearing before the Naval Aircrew Advisory Board. The Naval Aircrew Advisory Board should be brought in in those cases where there is an almost disciplinary angle, where, as in temperamental unsuitability, the problem is clearly not a medical one, or to advise on those cases where a man has to be permanently grounded on medical grounds.

Perhaps even more controversial, but no less important, is the question of interviewing wives. Until now it has been possible only to invite wives who have lived in the immediate vicinity to come in. In each case the interview has been successful. To extend invitations to wives who do not live locally would raise the question of

transport and accommodation charges but the expenditure would be very small relative to the possible benefits to be gained. It would seem to be an experiment worth making.

Air Marshal Sir Patrick Lee-Potter (London) asked why the Air Medical School had selected a 50/50 mixture of sea water and fresh water instead of a more dilute solution such as one-fifth sea water, as suggested by Ladell in 1943.

Surgeon Lieutenant Barrington replied that this decision was partly dictated by the results of the preliminary trial and partly because to advise survivors to add only a very small amount of sea water to their fresh water ration might be difficult to implement in a practical survival situation. Further work on more dilute solutions was required.

Air Commodore W. P. Stamm (Halton) asked whether consideration was given to retesting of category C aircrew in the pressure chamber in view of the possibility that the performance of some of them might improve.

Air Commodore W. Stewart (Farnborough) agreed that a man's tolerance of altitude might change with increasing age and weight, but in his experience the change was generally in an unfavourable direction and the retesting of people who had collapsed previously was nearly always regretted. He agreed with the Navy that they should not retest category C cases.

He asked whether the naval sea-water-drinking experiment supported the view of Gamble that if survivors lost 10% of their body weight their chance of survival was low.

Surgeon Lieutenant Barrington said that some of the subjects in this trial did lose 10% and they were all reasonably fit at the conclusion of the trial. This did not influence the conduct of the experiments; they continued whatever the body weight loss was, provided the clinical condition was reasonably satisfactory. The greatest loss was 11% of body weight.

Surgeon Captain Baskerville said that at the outset of the recent naval experiments he was one of the sceptics who considered that the drinking of sea water had been too strongly condemned. He was now, however, completely convinced that it is wrong to teach survivors to drink sea water under any circumstances whatsoever.

Surgeon Commander F. P. Ellis asked Surgeon Lieutenant Barrington if he had any concrete ideas as to the type of fundamental research which would throw further light on this problem.

Surgeon Lieutenant Barrington said he would like to know what goes on in and around the cell. Further studies to find out what happens to sodium and potassium inside and outside the cell in varying states of dehydration might be very revealing.

In conclusion, the **President** remarked what a great pleasure it was to him after many years of association with aviation medicine to see that research and development and training in the Royal Air Force and the Royal Navy were so closely and effectively co-ordinated.

'V-CIL-K'

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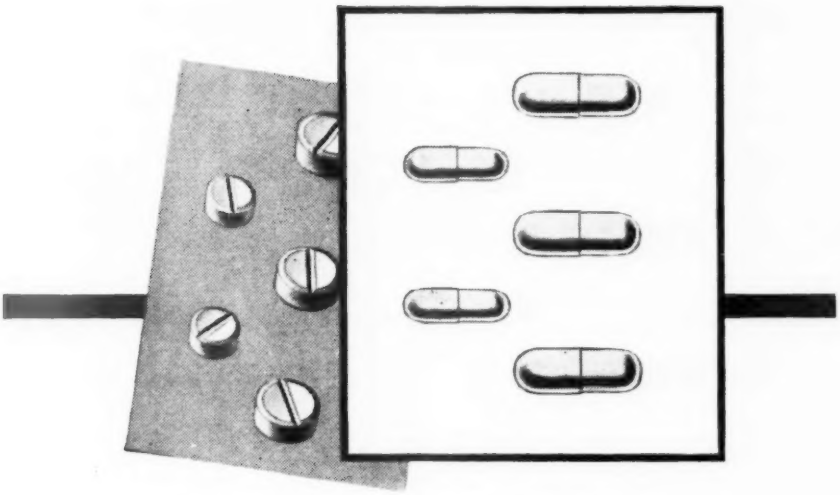

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Meeting
January 16, 1959

Cine-angiocardiography

By R. ASTLEY, M.D., D.M.R., C. G. PARSONS, M.D., F.R.C.P., and A. L. D'ABREU, O.B.E., F.R.C.S.

Birmingham

FROM August 1954, when cine-angiocardiography was first employed, until November 1958, 254 cine-angiocardiograms and 37 cine-aortograms have been made. The present analysis is concerned with the last fourteen months of the period, during which there have been 109 cine-angiocardiograms; the age distribution of the patients is shown in Fig. 1 and their diagnoses in Table I.

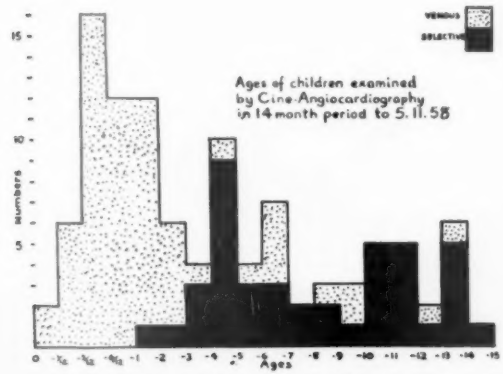

FIG. 1.—Age distribution of patients in 109 examinations.

TABLE I.—109 CINE-ANGIOCARDIOGRAMS IN 14-MONTH PERIOD TO 15.11.58

No gross defect	3
Dextroversion only	1
Septal defects	34
Septal defects with coarctation	3
Coarctation of the aorta	1
Eisenmenger's syndrome	2
Patent ductus arteriosus	14
Pulmonary stenoses (with or without shunts)	21
Fallot's tetralogy	16
Persistent truncus arteriosus...	2
Tricuspid atresia	1
Transposition of the great vessels	4
Confirming pulmonary vein enters left atrium	3
Confirming foramen ovale	2

Technique.—This has been described previously (Astley and Oldham, 1956; Astley, 1957). A Philips 5-in. image intensifier and 16 mm. Bolex cine camera are employed; a switch on the camera actuates the X-ray generator so that each cine frame is exposed for only two milliseconds, thus reducing movement blurring. The usual filming rate is 32 frames per second and typical exposure factors are $\frac{1}{4}$ or $\frac{1}{2}$ mAs per frame at 60–80 kV (27–36 inches focal-intensifier distance, using a stationary grid). A slow film is developed in an active developer.

The patient is premedicated by a modified form of the "lytic cocktail" (Rowe *et al.*, 1956), given one hour before the examination. For a venous angiocardiogram, the largest possible venous cannula is inserted beforehand. When the subject is positioned on the X-ray table, he may be sufficiently sleepy for the injection to be made without further medication; if he is still active, minimal intravenous thiopentone is given. Because of the short individual frame exposure times, only enough anæsthesia to keep the subject in position is required; respiratory or coughing movements do not matter. For cardiac catheterization followed by selective angiocardiography, the same premedication is used, supplemented by rectal thiopentone. Dosage of contrast medium is 1·5 ml. per kilogram body weight.

Patent ductus arteriosus is a particularly important condition in infancy, where the development of symptoms often means a poor prognosis. Clinically the diagnosis is frequently difficult at this age but cine-angiocardiography provides a quick and accurate method. It is suggested that every baby with symptoms due to a left-to-right shunt should be investigated to exclude this easily curable condition. The last 28 infants so examined have yielded 6 examples; altogether there were 14 children with a patent ductus in the series of 109 examinations under analysis.

The most typical and constant sign is a diastolic dilution defect in the enlarged pulmonary artery (Fig. 2). In the left oblique position the entry of non-opacified blood is first seen as a translucency in the contrast medium near the bifurcation. This extends, often as far back as the valve,

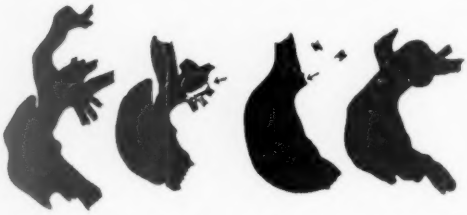

FIG. 2.—The characteristic intermittent filling of the pulmonary artery in patency of the ductus arteriosus (left oblique position). (1) The pulmonary artery fills with contrast from the right ventricle. (2) Dilution from the aorta begins. (3) The artery is empty of contrast back to the valve. (4) The pulmonary artery refills from the right ventricle and the cycle repeats.

giving an empty appearance that is followed once more by systolic filling from the ventricle; thus there is a very characteristic intermittent contrast filling and emptying of the pulmonary artery. Later when the left heart fills there is persistence of contrast in the artery and now a second (systolic) dilution defect, by non-opacified blood from the right ventricle, can sometimes be seen as a "bubbly" appearance under the aortic arch. Associated signs are a crescentic shape of the small right heart due to indentation of the septum by the large left atrium and ventricle, a rather large aortic arch and slower than usual left heart clearance. The main differential diagnosis is from a ventricular septal defect causing a dilution defect that is originating in the right ventricle but being propelled into the pulmonary artery.

Septal defects.—In infancy, the main value of the method lies in differentiating these conditions from a patent ductus; this is easily achieved with a venous injection in the left oblique position. A dilution defect is seen in the contrast medium in the right atrium or ventricle, indicating the left-to-right shunt. When the left heart fills, there is refilling of the right heart. The pulmonary artery is large and shows persistent filling; the aorta is small and often difficult to see. Sometimes in babies, even with a venous injection, there is a fleeting reverse flow, from right to left ventricle, in the early stages of the cycle.

After infancy, cine-angiocardiography is best employed in conjunction with cardiac catheterization and selective injections. If the catheter passes from the right to the left atrium, an injection into this chamber will show the size of the defect and readily distinguish an insignificant foramen ovale (Fig. 3). If the catheter enters a pulmonary vein it may be uncertain into which atrium that vein is draining; the behaviour of the contrast medium after a small injection during withdrawal of the catheter will readily elucidate

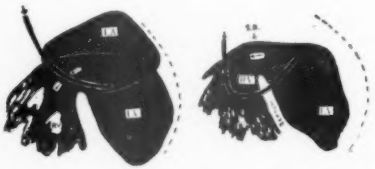

FIG. 3.—Isolated ventricular septal defect in a boy of 11 years, confirmed at operation (left oblique position). (1) The catheter tip lies in the left atrium but contrast medium only passes to the right after the left ventricle has filled, indicating that the catheter is through a foramen ovale. (2) The catheter tip is in the left ventricle; the return flow to the right shows a large septal defect.

this. With simple ventricular septal defects, small reverse shunts are frequently seen, even when right heart pressures are not very high (e.g. 40 mm.Hg systolic). These confirm the diagnosis and may indicate the exact situation and size of the defects (Fig. 4).

FIG. 4.—Isolated ventricular septal defect in a girl of 3 years; right ventricular pressure 45/0 mm.; findings confirmed at successful operative closure (left oblique position). (1) There is a reverse shunt seen as a single jet in only two frames. Its base indicates the size and site of the defect. (2) Dilution defect in the right ventricular outflow tract. (3) Left-to-right waves seen in the later phases.

Pulmonary stenoses.—Valvular, infundibular or combined stenoses are easily demonstrated by a venous or selective injection, preferably in the right oblique position (Fig. 5). (It is important to note that they are sometimes indistinguishable in the *left* oblique position.) A valvular stenosis is often accompanied by some degree of narrowing of the outflow tract, varying in calibre during the cardiac cycle and attributable to secondary muscular hypertrophy (Fig. 6). When there is a combined pulmonary stenosis and ventricular septal defect it is convenient to make two contrast injections, dividing the total dose; about one-third is injected into the outflow tract in the right oblique (Fig. 7) and the remainder in the left oblique position.

The timing of shunts.—A simultaneous ECG or pressure tracing, against which the moment of

FIG. 5.—Valvular pulmonary stenosis in a girl of 5 years (right oblique position). Venous injection; the stenosed valve initially transmits only a jet of contrast medium. Later, the valve appears as a dome of translucency below the dilated pulmonary artery. There is some early aortic filling due to an inter-atrial shunt.

FIG. 6.—Valvular pulmonary stenosis in a girl of 11 years (right oblique position). In addition to the dome of the stenosis, note the varying calibre of the outflow tract.

FIG. 7.—Fallot's tetralogy in a boy of 6 years (right oblique position). There is both infundibular and valvular stenosis. (A second injection in the left oblique position, not illustrated, showed the associated ventricular septal defect.)

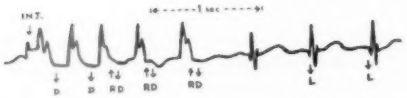

FIG. 8.—ECG record during cine-angiocardiography in a girl of 1 year with an isolated ventricular septal defect. The arrows indicate the timing of shunts (D = dilution defect due to left-to-right flow; R = reverse shunt, right-to-left; L = positive left-to-right waves).

exposure of each cine frame is recorded, allows the timing of events seen in the film. Fig. 8 shows such a record from a child where cine-angiocardiography (but probably no other method) permits the identification of ten shunts within three seconds.

Safety and accuracy.—There were no deaths amongst the 254 cine-angiocardiograms; in the fourteen-month series only one patient caused anxiety, fortunately temporary, the result of an erroneous injection into the coronary sinus. The safety of the procedure is believed to be closely related to minimal anæsthesia, permitted by the very short X-ray exposure times.

There have been a number of mistaken diagnoses, largely due to errors of observation (e.g. a left-to-right shunt through a ventricular septal defect was correctly diagnosed but an associated pulmonary stenosis, obvious in retrospect despite the fact that there was no pressure gradient across it on catheterization, was missed). The diagnosis of a patent ductus is considered to be highly accurate, making aortography rarely necessary except possibly in babies where it is combined with a septal defect. A venous injection will easily detect a simple septal defect, although its localization may sometimes be uncertain; a selective injection will localize a septal defect accurately and often indicate its size. It is possible to demonstrate shunts not shown by blood oxygen levels (e.g. in the Eisenmenger syndrome bidirectional shunts have been shown where catheterization did not reveal the left-to-right component).

Technical failures have been infrequent; two out of the 109 were complete failures, including one due to a catheter rupture.

Indications for full-sized films.—In general, our indications for large-film angiocardiography are twofold: when a larger field area is required (e.g. to show multiple collateral vessels) or when very small detail has to be demonstrated (e.g. there were four babies of low weight, all under eight weeks old, where there was possible pulmonary atresia). During the period under analysis, 20 angiocardiograms were carried out with a Schönander film changer, compared with 109 by the cine method; this is a measure of our preference for the latter.

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Cine-aortography for the Visualization of the Aortic Valve and Coronary Arteries

By Graeme Sloman,[1] M.R.C.P.
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With progress in the treatment of the diseased aortic valve more surgeons are favouring a direct vision approach. Open operation using hypothermia has been used in selected cases by Brock (1956, 1957), Lewis *et al.* (1956), and Lam (1958), and procedures utilising the pump oxygenator have recently been described (Lillehei *et al.*, 1958). An accurate pre-operative assessment of the anatomy and function of the valves would help in the planning of a direct operation. Twenty-five dogs were studied using cine-aortography to develop a technique suitable for application to patients with aortic valve disease.

Apparatus.—The cine-angiograms were performed using a 35 mm. Arriflex camera mounted on a standard 5-in. Philips image intensifier. A Philips D.C.X. generator supplied a smoothed current to the undercouch tube. A monocular viewer enabled the radiologist to see through the shutter of the camera during the filming. The contrast medium was injected rapidly using a mechanical injector. The electrocardiogram was monitored throughout and recorded on a photographic recording instrument during the injection of contrast medium. The R wave of the electrocardiogram was used to activate a simple mechanical marker which was photographed on the same cine film. The cine-angiograms were taken on 35 mm. film at 32 frames per second. After processing they were optically reduced to 16 mm. for analysis. 76% Urografin, 90% and 85% Hypaque were used as contrast media.

Development of a method.—Twenty-five mongrel dogs were studied in order to develop a method which was simple and safe. Under light general anæsthesia the right carotid artery was dissected and a NIH cardiac catheter was passed through the artery into the ascending aorta. The tip of the catheter was accurately positioned about 2 cm. above the aortic valve leaflets. The animal was turned into the left anterior oblique position for the angiogram. On analysis of the cine film movement of the valve leaflets was well demonstrated. No reflux of contrast medium occurred across the normal aortic valve. Nelson *et al.* (1958) also found on their studies on dogs that using a side-opening, closed-end catheter positioned in the ascending aorta 2–3 cm. above the valve, rapid injection of contrast medium did not produce false radiographic evidence of aortic regurgitation.

As well as obtaining a good idea of the anatomy and function of the aortic valve, we were always able to study the coronary arteries. When cardiac arrest was induced with acetylcholine before injecting the contrast medium the visualization of the coronary arteries was greatly improved (Fig. 1).

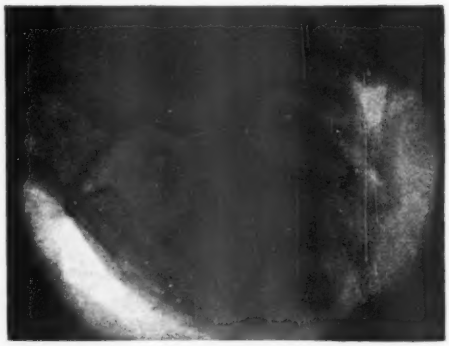

Fig. 1.—Injection of contrast medium into the ascending aorta during induced cardiac arrest to show improved visualization of the coronary arteries.

Clinical application.—Because of the limited size of our X-ray field using the image intensifier, our studies on the human subjects were confined to visualizing the aortic valve. The following indications are suggested for carrying out this procedure:

(1) In aortic stenosis and regurgitation, to study the movement of the aortic valve leaflets and to assess approximately any aortic regurgitation.

(2) In mitral valve disease, when an early diastolic murmur is heard at the base of the heart, cine-aortography should allow us to exclude aortic regurgitation.

(3) To define the anatomy of aneurysms of the ascending aorta or of the sinuses of Valsalva.

(4) To visualize the level of various forms of aortic fistulæ.

[1]Leverhulme Research Fellow, Royal College of Physicians, London.

Eight patients were studied. Under light basal sedation with intramuscular pethidine and phenergan and infiltration of the skin and subcutaneous tissue with local anæsthetic, the right brachial artery was exposed about 5 cm. above the elbow. A longitudinal incision was made in the artery and a No. 8 NIH catheter with four side holes and the end blocked was passed under careful X-ray control, using the image intensifier, into the ascending aorta and positioned with the tip about 2 cm. above the aortic valve. With the patient in the left anterior oblique position a test injection of approximately 5 ml. of contrast medium was injected rapidly by hand to verify the position of the catheter. 1 ml. per kg. body weight (maximum 50 ml.) of contrast medium was then injected rapidly (1 to 1·5 seconds) through the special NIH catheter, and films were taken at 32 frames per second. Carotid artery compression was not employed. No arrhythmias were experienced nor were the patients troubled by any serious subjective sensations. The artery was repaired satisfactorily in all patients.

Results.—Two patients with calcified aortic valves were studied and in those a clear picture of the movement of the aortic valve was obtained; in both there was a variable degree of aortic regurgitation as assessed by the amount of contrast medium that passed from the aorta to the left ventricle during diastole. It was noted in two patients with moderate to severe aortic regurgitation that there was unsuspected mitral regurgitation, as seen by reflux of contrast medium from the left ventricle to the left atrium during systole, in the absence of any induced arrhythmia.

Three patients with dominant mitral valve disease were studied. In one of these patients associated aortic stenosis was diagnosed, but the cine-aortogram, in addition to confirming the aortic stenosis, showed a moderate degree of aortic regurgitation. In a patient with mitral regurgitation and an early diastolic murmur at the base of the heart the cine-aortogram did not show any evidence of aortic regurgitation, so that the murmur was interpreted as being due to pulmonary regurgitation secondary to pulmonary hypertension. A third patient with mitral and aortic valve disease was studied to assess the amount of aortic regurgitation. The cine-aortogram showed a moderate degree of reflux into the left ventricle (Fig. 2).

Two other patients with severe aortic regurgitation were studied to assess the feasibility of a plastic repair to the diseased and deformed aortic valve. The cine-angiographic study suggested that a surgeon could obtain considerable information when a direct operation was being planned.

FIG. 2.—A frame from a cine-aortogram carried out on a patient with aortic stenosis and regurgitation.

Because of our limited field size we were only able to visualize the commencement of the main coronary arteries. When the field can be extended, visualization of the coronary circulation might assist in the diagnosis of chest pain when the electrocardiogram is found to be normal. In established coronary artery disease a coronary angiogram might also help with the prognosis and with the evaluation of various forms of long-term medical treatment. In those patients selected for a myocardial revascularization procedure, a pre- and post-operative coronary cine-angiogram would enable an objective assessment to be made.

Acknowledgments.—This work was carried out with the close co-operation and practical assistance of Dr. Keith Jefferson, Dr. Aubrey Leatham and Miss Denys Green. Mr. J. G. Davies designed and built the cine-angiogram marking device used in this study. I thank Dr. Roy Astley for his initial help with technical aspects and his continued interest in our work.

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Meeting
February 20, 1959

Occupational Mortality

By W. P. D. LOGAN, M.D., Ph.D.

London

ONE of the series of publications that the General Register Office is rather proud of, though in a humble way, is its decennial supplements on occupational mortality. We are proud because of the long history of these reports despite the labour involved in producing them, and we appreciate the attention they receive in this country and abroad. We are humble because we know something of the limitations of our methods and the inadequacies of our results.

In 1954 (Logan, 1954*a*, *b*, *c*) I told you something of the earlier history of our occupational mortality reports and presented results that had emerged in a preliminary study of deaths in 1950 related to a 1% sample of the 1951 Census populations. I shall not recapitulate this earlier history but get right on to my main theme, which is to talk about the results of the analysis of mortality in the five years 1949–53, related to the full 1951 Census population figures. These results have been published (Registrar-General, 1958*a*) in a 600-page two-volume report selling at seven guineas the set. At that size, and at that price, it has been suggested to me, as it was suggested to my two predecessors (Stevenson, 1923, 1928; Stocks, 1938) that a brief personal account of some of the contents would be a public benefit.

Let me first remind you of the method. We took the deaths in 1949–53 of men, married women, and single women, classified by occupation—in the case of married women by occupation of husband—and related these to the populations of these occupations as enumerated in the 1951 Census. The main source of error in the resulting death-rates is discrepancy between occupational description in the death registers and in the Census schedules, so that for particular occupations the deaths and the populations do not properly match. This is a difficult problem, and the cause of many statistical headaches.

There were 600 or so occupational groups by which the data were first classified, and these were condensed into the well-known social classes—five large categories of occupations based on their "general standing within the community", viz. I Professional, II Intermediate, III Skilled, IV Semi-skilled, V Unskilled. There was also some breakdown of these into a small number of sub-classes, and, for some purposes, a separate classification of occupations into 13 socio-economic groups.

As a simple means of comparing mortality between different occupational groups frequent use was made of the Standardized Mortality Ratio (S.M.R.) at ages 20–64, and the Proportionate Mortality Ratio (P.M.R.) at ages 65 and over. The S.M.R. compares the death-rate at 20–64 of, for example, men in a particular occupational group with that of all men of corresponding age distribution, the latter taken as 100; and the P.M.R. at ages 65 and over provides a proportionate mortality comparison for selected causes of death at ages 65 and over. At these higher ages a proportionate index is preferable, since discrepancies with a population denominator become rather large.

The report also analyses infant mortality and stillbirths.

The purpose of this paper is to give a few examples of the results that have emerged from the 1949–53 analysis.

Fig. 1 shows the social class distribution of male mortality from all causes in 1949–53 compared with 1930–32. The regularly rising gradient in the previous analysis has been replaced by a W-shaped arrangement—a quite unexpected finding, or unexpected, anyway, in 1954 when the preliminary sample analysis likewise gave this peculiar W pattern (Registrar-General, 1954). One possibility was that population transfers between the social classes might be responsible, and in the full report an attempt has been made to determine what effect population changes might have had.

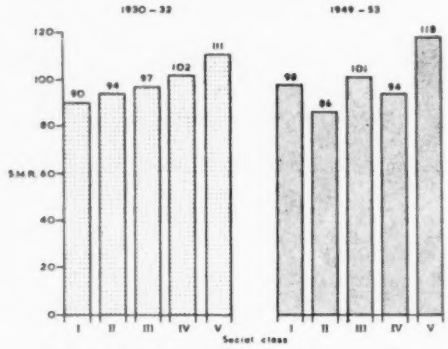


FIG. 1.—S.M.R.s all causes. Males 20–64.

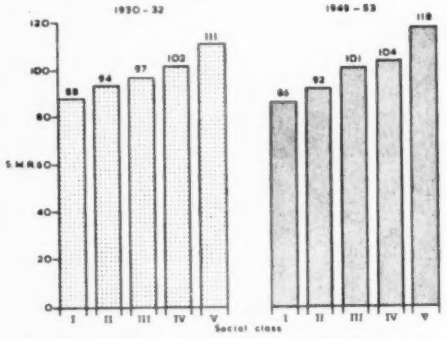
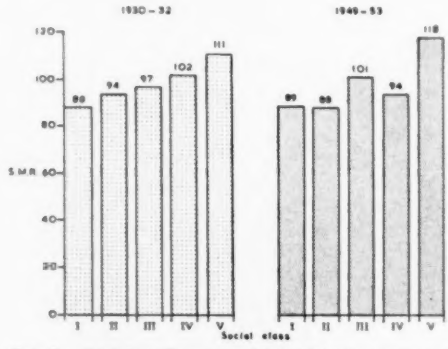


FIG. 3.—S.M.R.s all causes. Males 20–64. Company directors transferred from Class I to Class II and changes in Social Class composition between 1930–32 and 1949–53 allowed for.



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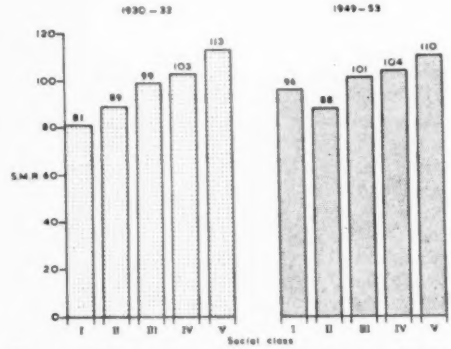

FIG. 4.—S.M.R.s all causes. Married women 20–64.

The result of adjusting the social class populations of 1951 to what they were, approximately, in 1931 was to bring up the S.M.R. for Social Class IV from 94 to 104, thus eliminating one irregularity in the trend (Table I).

TABLE I

	I	II	III	IV	V
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For comparison with men, Fig. 4 shows the social class distribution of mortality of married women. It shows for 1949–53 a discontinuity between Social Classes I and II similar to that for men and no doubt with the same kind of adjustment it could be eliminated as well.

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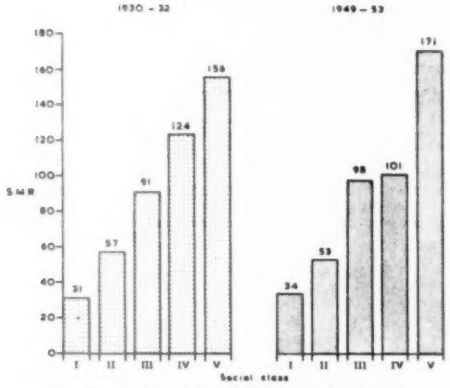

FIG. 5.—Bronchitis. S.M.R.s males 20–64.

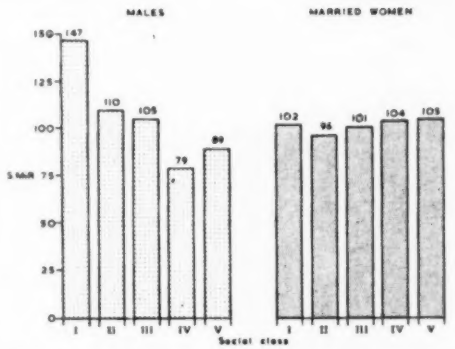

FIG. 7.—Coronary disease. S.M.R.s 20–64, 1949–53.

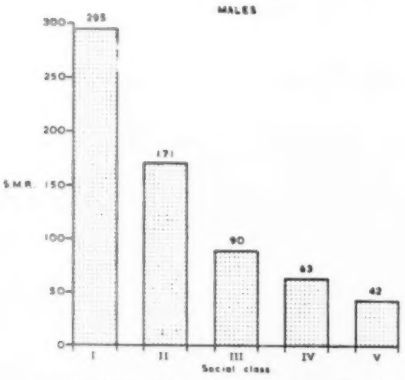

FIG. 6.—Poliomyelitis. S.M.R.s males 20–64, 1949–53.

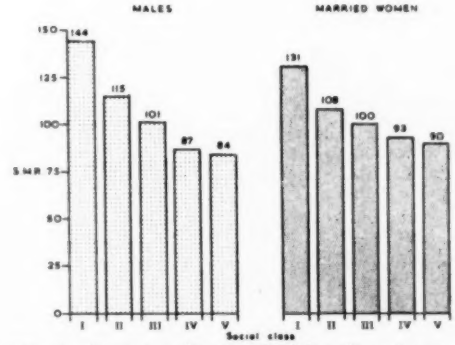

FIG. 8.—Coronary disease. P.M.R.s 65 and over, 1949–53.

Class I was seven times greater than of Social Class V (Fig. 6). A glance at a few selected occupations (Table II) shows that doctors and

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In contrast with coronary disease, mortality from myocardial degeneration (Fig. 9) is correlated with social class just as strongly in the opposite direction; and adding the two together (Fig. 10) gives gradients of S.M.R.s at ages 20–64 that go downwards from Social Class I for men, and upwards from Social Class I for married women.

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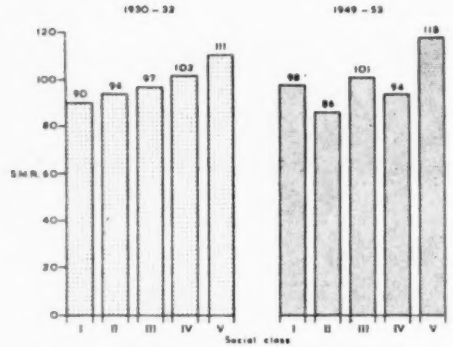

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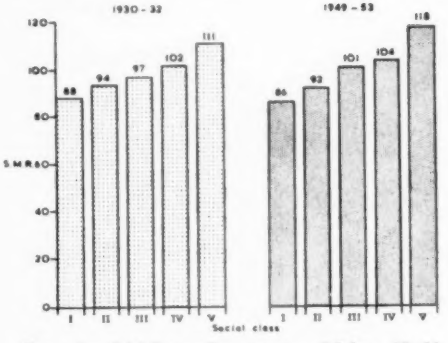

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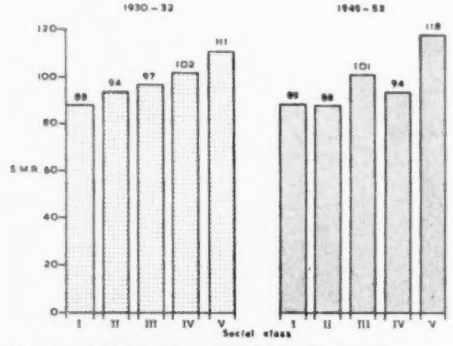

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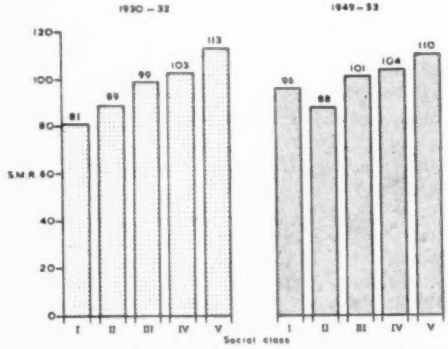

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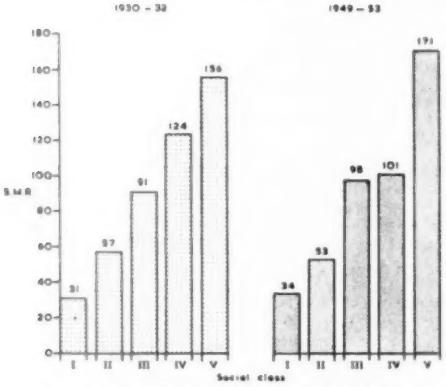

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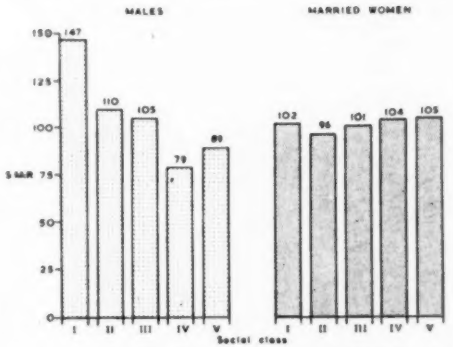

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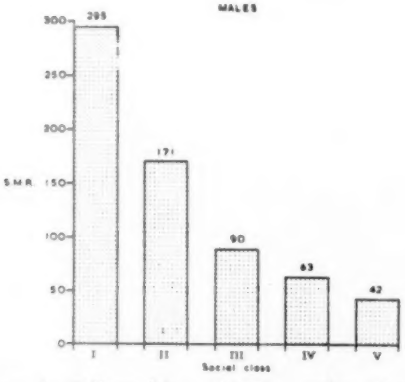

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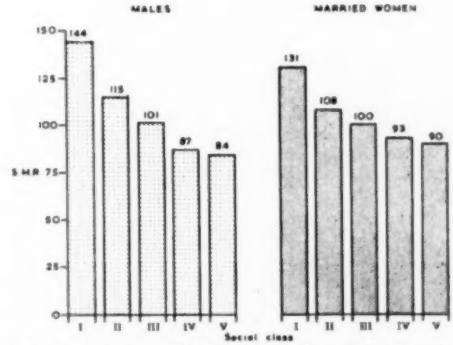

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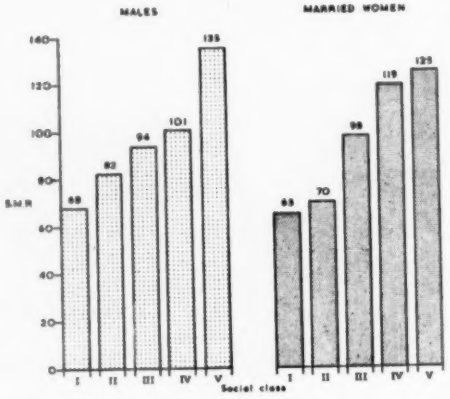

FIG. 9.—Other myocardial degeneration. S.M.R.s 20–64, 1949–53.

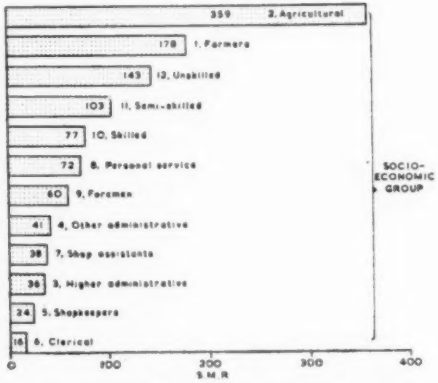

FIG. 11.—Cancer of lip. S.M.R.s males 20 and over, 1949–53.

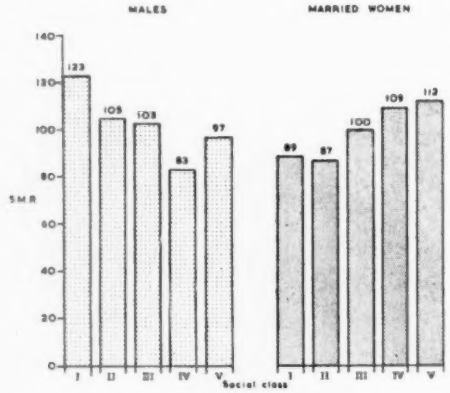

FIG. 10.—Coronary disease and other myocardial degeneration. S.M.R.s 20–64, 1949–53.

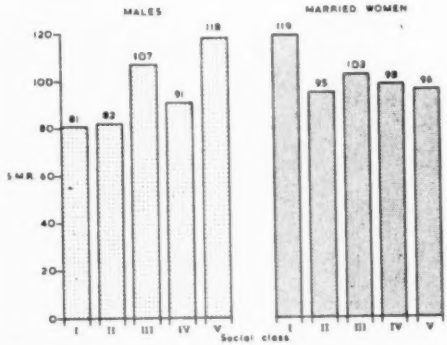

FIG. 12.—Cancer of lung and bronchus. S.M.R.s 20–64, 1949–53.

were included. I turned to one of these, giving cancer in socio-economic groups, and the first site to be analysed was lip. The result is startling (Fig. 11), indicating that the mortality risk in male agricultural workers aged 20 and over (S.M.R. 359) is more than 20 times greater than amongst clerks (S.M.R. 16). As regards proportionate mortality ratios for men aged 65 and over, almost every cancer site showed a social class gradient, eleven of them upwards from Social Class I to V and 18 downwards from Social Class I to V.

For cancer of lung and bronchus at ages 20–64 (Fig. 12) there was an upward gradient, not very strong, from Social Class I to V for men, and the suggestion of a gradient in the opposite direction for married women.

Cancer of stomach (Fig. 13) showed a much more definite and regular social class gradient, similar in each sex, and this was repeated for ulcer of stomach; but the gradient was not quite so regular for ulcer of duodenum (Fig. 14).

Cancer of cervix in married women (Fig. 15) showed a steep upward gradient for Social Class I to V. Frequency of child-bearing no doubt has something to do with this, but can scarcely explain the somewhat similar pattern amongst single women. In contrast with cervix, cancer of breast in married women showed a steep gradient in the opposite direction, i.e. downwards from Social Class I (Fig. 16). Again child-bearing and breast-feeding may partly account for this distribution, but how do we explain the rather similar distribution for single women?

This very definite contrast between cancer of cervix and cancer of breast has appeared also in

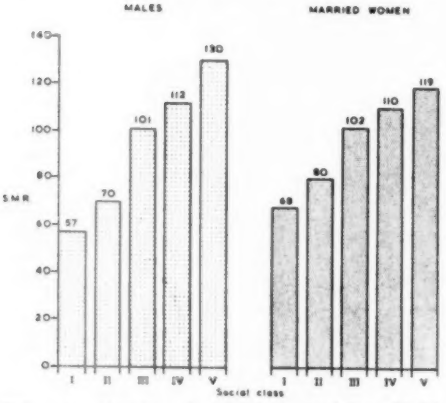

FIG. 13.—Cancer of stomach. S.M.R.s 20–64, 1949–53.

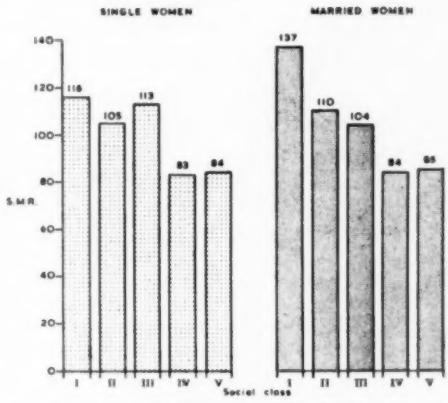

FIG. 16.—Cancer of breast. S.M.R.s 20–64, 1949–53.

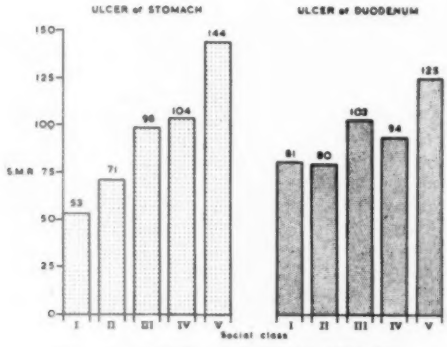

FIG. 14.—S.M.R.s males 20–64, 1949–53.

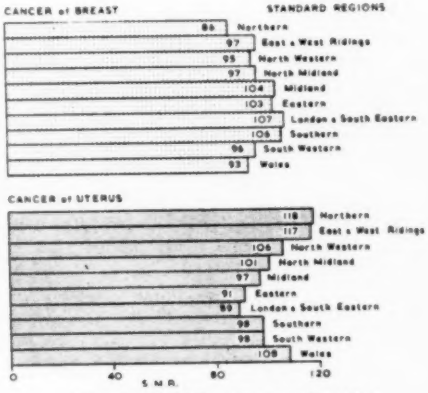

FIG. 17.—S.M.R.s all ages 1950–53.

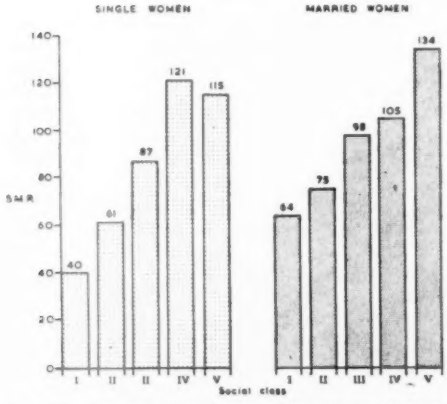

FIG. 15.—Cancer of cervix. S.M.R.s 20–64, 1950–53.

our 1950–53 Area Mortality analysis, another and separate part of the Registrar-General's 1951 Decennial Supplement. Cancer of breast was lowest in the Northern region (S.M.R. 86) and highest in London and the South East (S.M.R. 107); cancer of the uterus was highest in the Northern region (S.M.R. 118) and lowest in London and the South East (S.M.R. 89) (Fig. 17).

Standardized mortality ratios for maternal causes showed some quite large differences between the socio-economic groups (Fig. 18) ranging from 177 for wives of farmers down to 67 for wives of foremen. These ratios are based on populations, not numbers of births. The conventional maternal mortality rate per 1,000 births ranged from 0·63 in Social Class I to 1·08 in Social Class V.

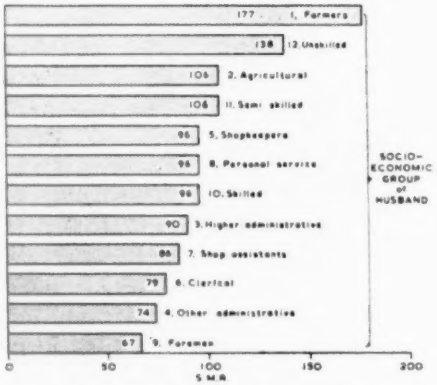

FIG. 18.—Maternal mortality. S.M.R.s married women 20–64, 1949–53.

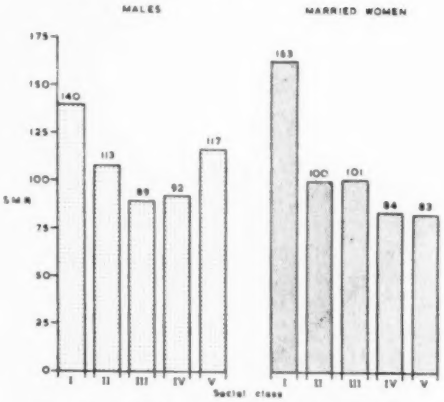

FIG. 19.—Suicide. S.M.R.s 20–64, 1949–53.

Finally we come to suicide (Fig. 19) where, for males, the social class distribution in 1949–53 was U shaped (high in Social Classes I and V) in contrast with previous analyses when mortality was highest in Social Class II followed by Social Class I, and below average in Social Class V. Possibly some juggling with company directors might change the relative positions of Social Classes I and II, but I cannot explain the rise of Social Class V. It has not happened with married women whose distribution (high in Social Class I, low in Social Classes IV and V) remains much as before, though with some worsening in the relative position of Social Class I.

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Section of General Practice

President—G. J. V. Crosby, C.B.E., M.D.

Meeting
November 19, 1958

DISCUSSION ON COLONIC DISORDERS

Dr. K. H. G. Milne (London): If we general practitioners classify diseases of the colon on the basis of their management, the first and easiest group seen is "the short and sharp" one—the green-apple colics of children, the acute food poisonings and other "D. & V.s" of adults, and the temporary constipation due to changing habits in the elderly. These are mere incidents in the life of the patient and after a brief course of treatment they can be forgotten. Secondly there are the major conditions, representing an ever-present source of trouble over months or years, and which may greatly modify the life of the patient; in this group are diverticulosis, ulcerative colitis and malignant disease. Finally, there is a third group, a hotch-potch of illnesses, which can also cause trouble on and off for years, but will interfere with the patient less, the more that we can arrange for their management to be played in a minor key. The most notable of these is spastic colon, grouped, for my purposes, with muco-membranous colitis and carbohydrate dyspepsia, &c., if these be true diseases in their own right at all.

In undergraduate teaching cases of suspected malignant disease must receive full investigation, merely on first suspicion, and no other attitude is really possible. Cases of diverticulitis and ulcerative colitis must also be fully investigated, early rather than late, so that they can be properly assessed and a long-term plan made for management, before they run into trouble. But this complete diagnostic scheme, with barium enema, sigmoidoscopy, pathological tests, &c., if given to a patient suffering merely from a spastic colon, will not only be a complete waste of effort, but will do positive harm, in that it will focus attention on symptoms, whereas our chief hope in treatment here lies in getting the patient to "rise above it all", and to learn to live with his condition understandingly. Such investigations may in fact sow the first seeds of fear of malignant disease, which will be the more difficult to eradicate later.

In a recent survey of his Cornwall practice, Davies (1958) found that one in every thirty-five attendances throughout a year was because of organic disease of the large bowel; as far as they are comparable, these figures agree with Fry's survey (1957), and I think they are typical. It would be safe to say that at least half of these would present no difficulty in management, for a general practitioner must send an acute abdomen to hospital, and the treatment of D. & V. in a previously healthy person is straightforward. But for every patient Davies saw in this organic group, he probably also saw one with symptoms that might equally well have sprung from disease of the colon, but whom he was able, in retrospect, firmly to assign to the functional or neurotic group. It is in the separation of these cases, where the history is vague and extends over many months, that there can be so much difficulty.

Can anyone confidently, and accurately, distinguish a spastic colon from an early carcinoma on the basis of the history and one examination? Muir (1956) analysed the presenting signs and symptoms of over 700 cases of carcinoma of the large bowel seen at King's College Hospital. About one in four presented with acute obstruction or with peritonitis; in the remainder, the common symptoms were pain, loss of weight, bowel upset, or faintness or lassitude. All these symptoms are very common in our surgeries. Bleeding *per rectum* in the absence of clearly culpable hæmorrhoids will always ring the alarm bell, but this was one of the least common symptoms: it occurred in only 6% of Muir's cases with a growth in the sigmoid, and became less frequent as the growth was found to be farther away from the rectum.

The chances are, I believe, that each of us will see one fresh patient with carcinoma of the colon in a year; but we shall certainly see one fresh patient a *week* whose symptoms could be due to a large bowel growth. Every general practitioner knows that the overall five-year survival rate for this condition can only be improved from its present figure of 45–50% if cases are detected earlier. But I think that many of us would agree that the sheer numbers involved, quite apart from the other considerations I have mentioned, make the investigation of every suspicious case impossible at the start, and each of us is acting, consciously or unconsciously, as a sieve. The diagnosis cannot be based only on the history or on the examination, but on both of these, and also on the early response to treatment.

There is no one symptom in the history that is going to raise the strong suspicion of malignancy,

although a recent but sustained alteration of bowel habit in a man of 50 would be a very suspicious single item. On the other hand, a strong correlation between abdominal pain and nervous or physical stress is strongly in favour of a functional disorder.

Typically, spastic colon is a disease of young women and it must be unusual for it to occur for the first time after 40. But then I remember a nurse of 30 whose presenting symptoms were due to an anæmia of 50%, and whose completely silent carcinoma at the hepatic flexure was found only when the anæmia was investigated fully. The evaluation of recent symptoms is often held to be the key, but how long is "recent"? The average time between the onset of symptoms and seeking advice in the case of carcinoma of the right colon is said to be nine months.

It does not do to labour the question of physical examination, except to point out that half the cases in Muir's series had a palpable mass when they got to hospital.

After the history and examination, there will be some patients who must quite clearly be investigated further; a few will stand out as needing only reassurance, advice and antispasmodics. But what of the middle three-fifths, who are the worrying ones, both for their general practitioner and for themselves? Surely it is justifiable to treat them for the innocent condition they may very well have for four to six weeks, and then to review them fully, in preference to sending them straight to hospital for investigation? Perhaps we should remember that many of the patients have come more for reassurance than for relief of symptoms, and that most of them will be entitled to this anyway.

I believe that this type of management will clear one's own mind about the patient, and that after review, in cases now felt to need investigation, it will be possible to encourage the patient to have the question pursued as far as is necessary. Once investigations are started, a negative barium enema by itself is not enough: out of 150 cases that came to operation at the Gordon Hospital (Ramsay, 1956) for carcinoma of the colon, 10 had not shown disease with a previous barium enema. In a case where a barium enema is asked for because of suspected carcinoma, and is found to be negative, ought not the doctor then to press for contrast air studies, or laparotomy, confident that investigations are not being done unnecessarily?

I realize that alteration of diet and other treatment given on a basis of spastic colon may relieve symptoms arising from a growth for a time, but I still believe that this is a reasonable course for a general practitioner to take, because he remains in touch with his patient, and can recognize early that things are not going as they should. I am sure that it is wrong to refer a patient to a consultant for a decision as to whether he should have investigations done; it is not fair to ask the consultant to decide on this point, since he is without the general practitioner's special knowledge of the patient, and also because he is denied our opportunity for reviewing the case, but must make up his mind at one interview. Once the general practitioner has referred a patient for a second opinion, he has almost invariably given his agreement to full investigation being done.

We as general practitioners are faced with a double duty: patients with malignant disease must come to treatment as early as we can manage it, but patients with functional disorders must be protected from the range of investigations that any mention of large bowel symptoms will evoke from the average hospital department.

I suggest that a reduction in the actual number of patients referred for investigation will let us help, in a positive way, those with functional conditions, and will clear the decks (and our own minds) for fuller investigation of the patients we know to need it.

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Sir Ralph Marnham (London):

Dr. Milne has made the point as to when patients with colonic disorders should be investigated, how much and by whom, and I would agree with him that in the less obvious cases a period of time should elapse before a patient is subjected to the full gamut of investigations which eventually are often necessary.

The symptoms which bring him to the doctor and from the doctor to the physician or surgeon are almost invariably some combination of alteration in bowel habit, constipation, diarrhœa, the passage of blood or mucus, any or all of these associated with some degree of abdominal pain.

The examinations to be carried out immediately are:

(1) *The abdomen*, where a spastic colon can usually be felt, apart from inflammatory masses or tumours, where a fullness in the right iliac fossa may be due to a distended cæcum from an obstruction in the sigmoid and where ascites can be diagnosed by feel long before fluid thrills and shifting dullness are very apparent.

(2) *Per rectum*, with special attention to the hollow of the sacrum and the state of the prostate or the pouch of Douglas as the case may be.

(3) *Sigmoidoscopy*, which should always be

done as part of the routine examination in the consulting room. In the vast majority of cases a preliminary washout and general anæsthetic are quite unnecessary. The former has an actual disadvantage as it will prevent excess mucus or blood coming down from above the sigmoidoscope being seen; the latter means admission to hospital or nursing home and builds up what, after all, may well prove a negative finding into something in the nature of an operation. Sigmoidoscopy should precede radiological investigation for the following reasons: (*a*) Residual barium sulphate may make it impossible. (*b*) Saving in time and money, be it the patient's or the tax-payer's. (*c*) The sigmoidoscope, as far as it goes, will give the more exact information. (*d*) It produces less physical discomfort. (*e*) It is rather humiliating to the clinician to have a carcinoma of the rectosigmoid junction diagnosed by the radiologist.

The investigation of these cases is completed by examination of stools for pathogens and occult blood and where necessary fæcal fat and undigested meat fibres, and lastly a barium enema.

It is not my province to discuss the treatment of constipation, be it due to atony or spasm, to stenosis, or diminished sensitivity of the lower third of the rectum, so that the arrival of fæcal masses does not excite the act of expulsion. I would only point out that in my opinion more people suffer from the effects of aperients than from constipation and that the insertion of a glycerin suppository every morning is likely to diminish rather than increase local sensitivity.

While diarrhœa is a symptom of many disorders of the colon its commonest cause, at least in this country, is intestinal hurry and a small barium meal and follow-through will often give valuable information on this point.

Blood and mucus are nearly always symptoms of organic disease and once the rectum and anus have been passed as normal the colon is the likely offender.

In this country the three common conditions which require surgical intervention are: Ulcerative colitis, diverticulitis and carcinoma.

Ulcerative Colitis

The indications for surgery in ulcerative colitis are at the present moment fairly clear cut; they have waxed and waned a good deal over the last forty years from the appendicostomy and cæcostomy of thirty to forty years ago, to ileostomy, a horrible operation before the advent of the polythene bag or some other self-retaining appliance. This was followed by the ileostomy plus colectomy and abdominoperineal in two or three stages, while to-day colectomy plus anastomosis of ileum to a short rectal stump is the operation of choice.

The indications for surgery are: (1) The acute fulminating type. (2) Failed medical treatment and chronic invalidism with the very real risk of carcinoma in any case persisting for eight to ten years. (3) Repeated hæmorrhage. (4) Multiple fistulæ with or without incontinence. (5) Stricture formation. (6) Extra-bowel symptoms such as arthritis and pyoderma.

The assessment of any case depends on the history, the sigmoidoscopic appearance and the X-ray appearances.

While ulcerative colitis has become more of a surgical problem, by which I mean a higher percentage of patients are operated on, the number of patients with diverticulitis who require operation is steadily diminishing.

Diverticulitis

Patients with diverticula present in the following ways:

(1) With abdominal discomfort and bowel irregularity, the passage of a little mucus and occasional diarrhœa. The treatment is a low residue diet, liquid paraffin for a very long period.

(2) With constipation, colicky pain in the left iliac fossa and malaise. On examination the temperature may be 100° F., and the pulse-rate 85. There may be a tender mass in the left iliac fossa—"a diverticula mass". Treatment is by bed, antibiotics, such as Achromycin, fluids only plus oily enemata and oil by mouth. Then the low residue diet regime follows. 90% clear up but however beneficial the effects of medical treatment are, these patients must always have a barium enema, repeated if necessary, to exclude a carcinoma as the primary cause. If the mass gets bigger, surgery is required, either to drain, to decompress by a transverse colostomy, or to excise.

(3) As acute or chronic intestinal obstruction.

(4) With vesico-colic fistula.

These last two conditions nearly always require staged operations.

Carcinoma

While in most of the other conditions the need for urgency when it exists is quite obvious, in carcinoma of the colon the urgency is there but the symptoms and signs may well be minimal. They are certainly varied. This is partly due to the fact that while anatomically we regard the colon as one organ it is in reality two with different developmental origin and function. The right half comes from the mid-gut and is concerned chiefly with water absorption. The left half comes from the hind-gut and is concerned chiefly with storage of solid fæces. The right half tends to produce a tumour which is

exuberant, ulcerates early and bleeds freely. The left half produces a constriction causing early obstruction. These will give a variety of symptoms and it is the exclusion or diagnosis of tumour which is one of the main reasons for early investigation.

In conclusion, it should be remembered that carcinoma of the colon can occur very early; it is not uncommon in the 20's. It may follow a polyp, single or multiple, and multiple polyposis, a condition which is almost always familial; at least 50% of these cases become malignant at an early age.

Treated early carcinoma of the colon carries a good prognosis but once glands are involved this alters materially. Hence the urgency, hence the care which has to be exercised. One barium enema reported on as normal does not of necessity mean a healthy colon; if symptoms persist investigations may have to be repeated, angry patients pacified, nervous patients reassured. Here I would put in a plea for explaining to these patients very carefully what you are doing and why you are doing it; most of them guess anyhow and if they feel you are being candid with them those who are passed as free from malignant disease are more likely to believe your assurances to this effect.

These cases are but another example of the importance of close contact being maintained between all the doctors engaged on them.

Dr. J. F. Stokes (London):

In a general medical clinic, with a gastro-enterological bias, the colonic disorders we most frequently see are those due to functional change and those associated with diverticulitis and with ulcerative colitis.

In this paper I shall comment on four points which I have found of interest in this field, namely:

(1) The relationship of diverticulitis to pelvic abscess.

(2) The difficulties provided by prolonged treatment of ulcerative colitis by corticosteroids.

(3) The diagnosis of ileocolitis.

(4) The management of functional colonic disease.

Diverticulitis.—In an ageing population we must expect to find more illness as a result of degenerative diseases, amongst which diverticulitis may reasonably be classed. When inflammation occurs in a diverticulum in the sigmoid colon (the commonest site of diverticula) it is not usually difficult to reach a diagnosis on the basis of left lower-quadrant tenderness and rigidity, fever and leucocytosis. Difficulties arise in the more spirited section of the population, who regard constipation as their birthright, and attribute their abdominal pain to the doubtful habits of a cook, the Government, or the vagaries of the Meteorological Office. As the inflammation advances in this group it is commoner, in my experience, for them to develop a pericolic abscess than a frank perforation; often this occurs in the area of the rectosigmoid junction and may escape notice until it achieves a considerable size or points and partially discharges itself, sometimes *per rectum* but perhaps more commonly *per vaginam.*

If a barium enema fills the abscess cavity with radio-opaque material, then the origin of the abscess is fairly clear, but often the abscess is walled off and radiography simply demonstrates the presence of diverticula. It is under these circumstances that we find ourselves at a disadvantage.

Miss P., aged 57, developed diabetes mellitus in 1955 and this was well controlled by diet until a recurrence of symptoms in 1958 suggested that some fresh complicating disease had arisen. Clinical examination showed fever and a mass palpable *per abdomen* and *per rectum.* Barium enema showed that this mass was pressing on the cæcum and occupying most of the pelvis and that there were many diverticula in the sigmoid colon. After a few weeks an abscess burst into the vagina, the fever settled and she felt much better. Subsequent laparotomy, however, and biopsy of the upper part of the mass revealed the presence of a carcinoma, probably arising from an ovary.

Carcinoma of the colon may, of course, present with a pelvic abscess and the correct diagnosis is sometimes obscured by the biopsy report. It is important to remember that the histologist is not always the ultimate arbiter of the nature of disease.

Mrs. L. S., aged 66, presented in 1956 with low intestinal obstruction due to a large pelvic mass. Barium enema showed an almost complete block in the lower sigmoid colon but enough barium got through to outline numerous diverticula in this region. Biopsy material taken from the mucosal surface of the stricture showed "colloid carcinoma". Two and a half years later the steady advance of her cerebral arteriosclerosis made it necessary for her to be looked after away from home. She could not go to an old people's home with a label of "carcinoma" nor to a home for the dying for which she clearly did not qualify. This difficulty of disposal could be overcome only when re-examination, both clinical and histological, had shown that she probably never had a carcinoma at all.

These two cases illustrate the diagnostic difficulties provided by pelvic abscesses when diverticula are shown to be present in the colon. Large pelvic inflammatory masses, masquerading as cancers of one sort or another, may often be due to diverticulitis and we should be very cautious in prognosing on these cases.

Corticosteroid treatment.—Now that so many patients receive corticosteroids, it is likely that most of us have at one time or another had experience of some of the complications of their prolonged use.

Moon-face and acne are of little account, sodium retention and hypertension may be of some nuisance value in older patients, exposure of latent diabetes, quiet sepsis and gastro-intestinal bleeding at any age, and the occasional extreme weakness associated with muscle wasting in a patient in negative nitrogen balance may be difficult to counter.

In ulcerative colitis they carry special risks. There is a danger of post-operative collapse when ileostomy is undertaken in a patient who has had a long pre-operative course of corticosteroids. Operation on a patient receiving corticosteroids always increases the corticosteroid requirement, and the risk can be avoided by stimulating the patient's own adrenals by corticotrophin pre-operatively and by giving extra hydrocortisone at the time of operation.

I want to call attention to another difficulty, exemplified by Mr. F., aged 28, who became apparently obstructed while on corticosteroid treatment five months after extensive ulcerative colitis was demonstrated in May 1956. X-rays of the abdomen showed many fluid levels and he became extremely ill.

Under these circumstances it is difficult to know for certain why abdominal distension has occurred. Perforation is well known to arise under corticosteroid treatment and the clinical picture is usually atypical. Distension due to ileus may be the first sign.

If the stool volume is high there may be gross potassium loss and hypokalæmia may result in dangerous distension. Œdema of the colon due to worsening of the disease despite the suppressive action of corticosteroids may also produce this picture.

A low potassium state may be fairly easily excluded, but the decision as to whether to increase the dose of corticosteroids on the assumption that there is an exacerbation of colitis present, or to withdraw the drug in the belief that perforation has occurred may be a matter of inspired guesswork.

Obstruction, whatever the cause, must be overcome as expeditiously as possible, since the gut is friable and liable to perforate when distended for any reason.

In this case we tailed off the dose under antibiotic cover and were lucky in that he made a good recovery and returned to full work; his obstruction was presumably due to mucosal œdema.

Ileocolitis is a rare disease but, like many rare diseases, is not difficult to diagnose if its possibility is kept in mind. A full description is given by Cooke and Brooke (1955).

Mrs. R., aged 28, complained in 1952 of weakness, weight loss, vomiting when under emotional stress, and irregular menses. She had always been constipated and had taken vegetable laxatives for fifteen years. She was under psychiatric treatment and the advice of a physician was sought because of weight loss. The sedimentation rate was raised at 30 mm. in the first hour (Westergren) and, in the absence of a clear reason for this, the gastro-intestinal tract was investigated radiologically and typical changes of ileocolitis were seen extending from mid-transverse colon to the terminal ileum; the distal half of the colon was normal.

Mrs. S., aged 42, developed weakness, weight loss, ulcers in the mouth and amenorrhœa in 1957. She was treated with prednisone on the assumption that she was suffering from Behcet's syndrome. Repeated bleeding *per rectum* was thought to be the result of corticosteroid treatment.

She was ill and thin, with a palpable thickening of the cæcum and a sedimentation rate persistently raised at 50 mm. in the first hour (Westergren). She denied any diarrhœa except at the times of her intestinal hæmorrhages. Barium enema showed changes of ileocolitis between the terminal ileum and mid-transverse colon with much distortion of the cæcal mucosal pattern. The mouth ulcers responded well to local hydrocortisone hemisuccinate.

Diarrhœa has been stressed as a presenting symptom in most reported cases; under these circumstances both small and large bowels are naturally investigated. In neither of these cases was diarrhœa a leading complaint and it was the absence of frequent bowel motions which had delayed diagnosis. In both cases it must be assumed that sufficient colon remained intact to carry out its normal drying and storing functions.

The illness of the first patient had been considered to have a psychogenic basis. The signpost to the necessity for deeper physical examination was provided by a raised erythrocyte sedimentation rate. The E.S.R. is a difficult investigation to assess and a rise in older people may be of little significance, but in young persons who are neither menstruating nor pregnant and who are not obviously the seat of focal infection, any abnormality should always be pursued. The diagnosis in the second case was delayed by the fixation of an exotic eponymous label which many sensible doctors had not felt able to challenge.

"*Spastic colon.*"—This syndrome comprises constipation, excessive mucus in the stools, spasm and pain in the colon muscle (often confined to the sigmoid) and pain and tenderness over a consequentially distended cæcum. By the time the patient seeks medical advice, a habit of over-purgation has, as a rule, been established.

This state of affairs is unfortunately common, and though it usually stems from anxiety its treatment on most occasions must lie in the hands of general physicians without resort to formal psychiatric assistance.

The first step in treatment must be to reassure both the patient and oneself that there is no organic obstruction in the colon, to clear the rectosigmoid junction whose anatomy may escape the attentions of the most enthusiastic rectal finger, even at the expense of the irradiation which a barium enema inevitably implies. The colonic distension which both the preliminaries and the actualities of a barium enema provide may, in fact, produce temporary improvement in symptoms.

Once this is done we have to assess, as we do in any psychosomatic disease, the relative importance of environmental circumstances and personality defect in its production, while using spasmolytic drugs and benign aperients in an attempt to achieve peripheral symptomatic control. Moral support and tolerance are quite as important as Pro-Banthine and belladonna in these circumstances.

I would like to suggest that in some older patients, those in whom psychological depression lies behind their constipation and pain, electroconvulsive treatment may be worth consideration.

Mrs. R., aged 72, had "always" been constipated and had suffered from pain in the left lower abdominal quadrant for six years before I first saw her in 1956. Barium enema showed diffuse spasm in the sigmoid and descending colon. Orthodox treatment produced little improvement and her depression, which had always been in evidence, worsened. In the belief that this might be contributing materially to her constipation and spastic colon, she was given a course of electroconvulsive treatment and has remained symptom free for eighteen months.

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Meeting
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The M.R.C. Grey-wedge Photometer—Its Use in General Practice

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DURING the Second World War the Medical Research Council undertook a survey of the hæmoglobin levels of different groups of the population, using the Haldane method of estimating hæmoglobin. The method adopted eliminated most of the instrumental errors, and so opportunity arose for the first time to assess the variability of the different observers taking part in carrying out hæmoglobin estimations by the Haldane technique.

The results showed a variability so great—over 10%—that reinvestigation of the whole problem of clinical hæmoglobinometry was necessary.

The older conventional methods of hæmoglobinometry suffered from the serious drawback that in every case the observer had to compare a standard colour with a test sample, the colour of which was altered progressively until it appeared to match the colour of the standard: but when a colour is altered by dilution, the amount of light that solution transmits is also altered; reduction of brightness leads to apparent alteration of colour.

In the Haldane and Sahli hæmoglobinometers the absence of achieving a brightness match before progressive alterations in colour by dilution constituted a serious difficulty: Macfarlane (1945) showed that even skilled observations using these methods could be 10% in error, relative to iron analysis as a base line. Also, even a slight degree of colour blindness in the observer led to significant error.

The M.R.C. investigation showed additionally that oxyhæmoglobin was the simplest derivative to prepare and that it was more reliable than acid hæmatin or carboxyhæmoglobin, the two favoured derivatives at that time (1945).

A new instrument was needed, free from these weaknesses, utilizing oxyhæmoglobin. The visual instrument eventually designed for the purpose was portable, and capable of being used by unskilled observers. In principle it is intended to measure the optical density of coloured solutions: under suitable conditions the optical density of a solution is proportional to the concentration of coloured substance it contains, and so this apparatus, the M.R.C. grey-wedge photometer, is suitable for measuring the amount of hæmoglobin in blood (King *et al.*, 1948; MacFarlane *et al.*, 1948). It can equally well be used to determine the concentration of other constituents of blood, urine and cerebrospinal fluid (King *et al.*, 1951).

I shall now describe briefly those conditions found in general practice in which the presence or absence of anæmia found at the time of examination is of value in the immediate treatment of the patient. The presenting symptoms of anæmia are mainly debility, dyspnœa,

palpitations, angina, headache, recurrent faintness, and œdema of legs. A significant proportion of patients estimated by many to be as much as one-third of all cases—present with symptoms due to anxiety, suppressed or florid. At the time of clinical examination therefore a normal hæmoglobin level is of considerable value in excluding anæmia as a cause, and directing attention elsewhere. Patients who show a hæmoglobin of 70% (10 grams/100 ml.) or less need further detailed examination by the pathologist.

With these factors in mind a division into two broad groups can be made:

(1) Women aged 20–50. In this group the commonest conditions are: (*a*) Nutritional iron-deficiency anæmia—the housewife's syndrome. (*b*) Pregnancy iron-deficiency anæmia. The hæmoglobin can easily be checked at routine antenatal examinations: when the blood pressure has been estimated and the diastolic pressure recorded a narrow-bore needle attached to a dry syringe is quickly inserted into a vein in the antecubital fossa and a few millilitres of blood withdrawn rapidly. On removal of the syringe and after the cuff has been removed it is rare for bleeding at the extraction point to be evident. By the time the patient is dressed her hæmoglobin has been accurately estimated. (*c*) Blood loss of significant degree due to too frequent or too heavy "periods". (*d*) The anæmia of rheumatoid arthritis.

(2) The second broad group is that of adult and elderly males in which the following conditions are found: (*e*) Angina in which the presence or absence of anæmia may be of material import. (*f*) Traumatic blood loss. (*g*) Epistaxis: the presence of anæmia of severe degree will affect the patient's treatment. (*h*) The silent bleeding duodenal ulcer in which the presence of severe anæmia is not unknown. (*i*) Hæmorrhoids, in which there can be considerable blood loss with consequent anæmia.

In both sexes Addisonian anæmia, cirrhosis of the liver, splenic anæmia, leukæmia, aplastic anæmia, tuberculosis, the rare myasthenia gravis, and malaria in non-Europeans may give rise to symptoms or signs of anæmia. The practitioner considering one of these rarer diagnoses in an individual case will find the immediate estimation of an accurate hæmoglobin of considerable help.

Malignant disease.—Cancer, wherever sited, may present with the symptoms or signs of anæmia. Whilst the estimation of an accurate hæmoglobin is of value at the time of examination, once the possibility of this diagnosis has given rise to disquiet in the family doctor's mind, his prime duty is to refer his patient at once for the fullest possible examination.

I hope this brief description of the usefulness of the M.R.C. photometer will have shown how necessary it is to the thoughtful practitioner. The advantages of being able to assess immediately and accurately his patient's hæmoglobin will be self-evident to the country doctor: whilst for those nearer a pathology laboratory there are considerable advantages for the patient. Unnecessary journeys costing time and money can be avoided. Demands on the laboratory can be lessened. The initial cost of the apparatus may militate against its immediate acquisition, but once acquired its usefulness more than justifies this when spread over a working life of many years. The overall cost, spread over twenty-five years, is less than a penny a day.

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Tape Recordings in Postgraduate Education

By JOHN C. GRAVES, L.R.C.P., M.R.C.S.
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I AM going to discuss some of the ideas that led to the formation of the Medical Recording Service of the College of General Practitioners (Graves and Graves, 1958).

Whenever I start talking about recordings, I am asked what is the matter with reading? Obviously most of our learning must come from reading; but if we consider a medical student's education, we see that his reading is planned round a framework of auditory teaching, including formal lectures, to which he just listens, bedside demonstrations at which he may ask questions, and rag classes to which he must contribute himself. Reading is needed to amplify this teaching, but cannot replace it. Indeed, Joyce and Weatherall (1957) have shown that students who worked by unsupervised reading only did less well than others who had lectures or discussion classes.

If this is true of students, how much more so must it be of general practitioners. With every year after qualification come more changes, not only of treatment but of concepts, which seem more and more strange to the older man. Such things as exposure treatment of burns, heart-valve surgery and electrolyte replacement therapy

gradually progress from dangerous new theories to accepted practice. If one lives and works in an atmosphere where these things are constantly discussed, this progress of new ideas is imperceptible, but for those who are isolated from the academic world it is very easy to cling unconsciously to the ideas current in their student days, and to dismiss as "small print" the incomprehensible new things.

It is quite possible for a conscientious general practitioner to read several journals and attend courses without ever realizing his own limitations, because he concentrates on those subjects that interest him, and finds boring those which he does not understand very well. In order to discover the gaps in his knowledge and plan his reading accordingly, he needs frequent discussion with other general practitioners.

Tape-recording can supply the missing auditory factor in postgraduate education, and help to encourage discussion. It will not do merely to read aloud material that has been designed for print, which may be very concentrated and difficult to understand on first hearing. Informal talks by experts who can give a general picture of what is going on in their field serve to remind listeners of changes in attitude to, for instance, the treatment of shock, and can introduce them to new drugs coming into general use. The strange thing is, that having heard a word like "mecamylamine" spoken, one is more prepared to read about it and even use it oneself, because it seems more familiar. Perhaps the most helpful kind of recording is that where the listener can feel that the speaker is talking and explaining his points to him personally.

However good the illusion, this is not *really* informal discussion. For that, you need other people—preferably more or less your equals, with whom you can argue—and not too many of them. You really need a group of fellow general practitioners, but it is not easy to get them together without some excuse. Our recordings provide this opportunity. Half-an-hour's lecture, followed by perhaps an hour of discussion, gradually giving place to more general talk in the comfort of your own home—surely this is one of the best ways of keeping up to date and of keeping in touch with your colleagues as well. We are always hearing of new study groups of this kind, and we are sure that many of these listeners are being spurred to read their journals more thoroughly so that they can shine at the next meeting!

But what of the doctor who lives miles from anywhere and has no neighbours? He can join in discussions on tape. Listeners with tape-recorders all over the country pass these talks from one to another, adding their own comments and questions which will be answered eventually by the speaker. The resulting discussion gives an insight into the problems of widely differing kinds of practice, and views are exchanged by doctors hundreds of miles apart who are unlikely ever to meet.

All this is mere justification for the use of tape at all, showing that it can be as useful as printed matter. There are many other obvious advantages: you can hear a famous speaker who might never visit your district in person, or you can hear a lecture that a surgery obliged you to miss. But there are instances where tape-recording can do things that print cannot, that is, reproduce the *sounds* of medicine. Firstly, the obvious example, heart sounds. Even for formal teaching, heart recordings have many advantages; many can listen at once, and the teacher can be sure that they are hearing the right sounds. The patient need not be subjected to repeated examination—he may be cured, or even dead, or one may hear his chest sounds before and after operation.

Secondly, the voice of the good teacher explaining a visual phenomenon such as a slide or picture! Your eye is free to look at whatever it is without having to run up and down the text, while the lecturer tells you all about it. This is probably the greatest argument in favour of any kind of auditory teaching.

Thirdly, the voice of the patient, which can often convey in a few words an impression difficult to describe in pages of print: Not only the quality of the voice, but also the expression, tone and emphasis can give important information about the patient and his illness which is difficult to obtain in any other way.

Lastly, the voices of the great men of medicine: We can only imagine what the giants of the past sounded like, but we can ensure that future generations will be able to hear the great men of to-day, such as Dr. William Pickles, the first President of the College of General Practitioners and long connected with this Society.

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JOYCE, C. R. B., and WEATHERALL, M. (1957) *Lancet*, ii, 402.

Dr. Graves' talk was illustrated by extracts from several recordings which are being circulated by the Medical Recording Service among members of the College of General Practitioners:

Mr. V. J. Downie, F.R.C.S.: "Shock."
Dr. M. Hamilton: "Modern Drugs in the Treatment of Hypertension."
Dr. C. A. H. Watts: "The Scope of Psychiatry in General Practice."
Dr. H. Farquhar: "Some Normal and Abnormal Heart Sounds."
Dr. J. R. Simpson: "Diagnosis and Treatment of Dermatitis and Eczema."
Dr. W. Pickles: A Presidential Address.

Myalgia in Bornholm Disease

By W. O. Williams, M.D., B.Sc.
Swansea

This paper is based mainly on my experience of Bornholm disease in the last three years, and in particular of an epidemic which occurred in Swansea in the summer of 1956.

Definition.—This disease is an acute febrile illness, characterized by the sudden onset of myalgic pain, accompanied by intermittent fever, anorexia, profuse sweating and frontal headache. The average duration is about three days but it may last as long as three weeks, with the patient returning to good health with amazing rapidity. There is no doubt that by far the most outstanding symptom in this disease is a pain of muscular origin. It may affect any voluntary muscle but favours the costodiaphragmatic group which is, of course, that primarily concerned with respiration.

Onset of pain.—The onset was quite sudden, often dramatic, and sometimes creating in the household an atmosphere of impending disaster. As pain was usually the first as well as the presenting symptom, it was not surprising that the patients sought medical advice early in the illness. In the Swansea epidemic, out of 74 cases studied, 22 were seen on the first day of their illness, 19 on their second, 16 on their third and remaining 17 tapering off in diminishing numbers over the next five days.

In only 8 patients were there other symptoms preceding the myalgia. These included a sore throat, anorexia, lassitude, rigors and mild rhinorrhœa, but in each case, pain followed in a few hours.

The pain often started as a result of muscular exercise, for example the housewife doing her daily chores, or the child running home from school. In some of the small children, however, the pain was first felt in the early hours of the morning, and their parents would find them sitting up in bed crying, and bathed in perspiration. This type of onset is interesting in relation to muscular exercise, because the diaphragm is the only voluntary muscle which is constantly at work during sleep. Furthermore, it is my experience that there is often, in very small children, an increase in respiratory rate in the presence of high fever from any cause. I believe, therefore, that the pyrexia in these children caused an increase in respiratory rate, even in sleep, and in turn precipitating diaphragmatic myalgia which would be severe enough to wake them up.

Character and severity.—The different descriptions of the pain given by various writers show that its severity varies from patient to patient and from epidemic to epidemic. Sylvest (1934) said that Finsen, who first described the disease in Iceland, described an outbreak of "an epidemic of stitch in the chest" whilst Dabney (1888), in the U.S.A., said that the people of Charlottesville had given it the rather frightening name of "devil's grip". This suggests that the pain can vary from a mere stitch to a very severe pain and this was found to be true in Swansea, but the "devil's grip" predominated.

It is difficult to convey to others the severity of pain. This cannot be measured in volume or weight, and adjectives, although helpful, are not sufficient in themselves. The first useful guide to the severity of pain, from any cause, is its description in the patient's own words. One patient described it as vice-like and another said that it took her breath away. One remark by a patient was "I don't mind admitting, I was frightened, and I really thought my end had come". The best method of assessing the degree of pain, however, was to ask them how it compared with other severe pain they had experienced. A patient who had had a typical attack of coronary thrombosis two years previously said that the pain of Bornholm disease was almost as severe, but that he did not feel quite so ill in himself. Another patient greeted me in the bedroom with this remark: "I have had another attack of pleurisy, doctor." One of the women who had experienced childbirth said quite seriously that she preferred a confinement to Bornholm disease. In this epidemic, the pain was divided into three degrees of severity. It was severe in approximately 60% of the patients, moderate in 30% and mild in only 10%. More females suffered a severe degree of pain than males, 74% as compared with 45%. In children under 3 years of age, the pain was particularly severe and made clinical examination, and indeed diagnosis, very difficult.

Duration.—The myalgia lasted anything from a few minutes to a whole day. When it lasted a long time, it was by no means constant but fluctuated in severity, varying particularly with the amount of work performed by the affected muscle. Another important characteristic of the pain was its tendency to recur after a period of apparent recovery. The interval of time between the seizures of pain varied from a few hours to two days. It is remarkable how well these patients felt during a remission. One little girl, for example, felt well enough to go bathing after recovering from her first seizure of pain.

Distribution of myalgia.—Although the distri-

bution was by no means constant during the course of the illness, it was most commonly located in the chest and upper abdomen. The distribution of pain in the 74 patients in the Swansea epidemic was: Subcostal and upper abdominal in 73, chest wall in 22, left shoulder in 2, right shoulder in 1, lower abdomen in 3, generalized myalgia in upper and lower limbs in 1.

Pain of subcostal and upper abdominal distribution was present in all but one patient. Warin *et al.* (1953) describing the Oxford epidemic, said that abdominal pain was more commonly felt on the right than the left. My findings showed the right side to be twice as commonly affected as the left.

Pain in the chest wall seemed to be either superficial or deep. When superficial, it was felt along the intercostal spaces and when deep it extended across several ribs and sometimes crossed the sternum to the other side. In several patients the intercostal pain was referred to the same segment of the abdominal wall, in the same way as pain in the shoulder in cases of diaphragmatic myalgia was referred from the ipsilateral side of the diaphragm.

It is possible that the deep pain might be due to the involvement of one of the deeper muscles of the chest wall, or that it might not be a myalgia at all, but a spread of inflammatory processes from the intercostal muscles to the parietal pleura. When deep pain was felt in the upper part of the sternum, the patient indicated the site either by placing the hand over the manubrium sterni or pointing the finger downward into the suprasternal notch.

The external ocular muscles may be involved in the myalgia; pain is felt on moving the eyes and even in one part of one eye. This was first brought to my notice by a Dublin general practitioner who reported to me an epidemic which had occurred in his practice in 1956, when I carried out a retrospective survey of Bornholm disease in the British Isles, on behalf of the College of General Practitioners (1957). Since then I have seen 2 patients in the same family with this type of myalgia.

Of 3 patients with lower abdominal pain, in only 1 did it remain in this part of the anatomy; in the other 2 it moved to the subcostal region. This brings me to another interesting aspect of the myalgia.

Variation of the site and extent.—The shifting character of the pain has been described by various authors, Dabney (1888), Hamburger and McNeil (1947) and Warin *et al.* (1953). In my clinical analysis in the Swansea epidemic, approximately 49% of the patients showed this phenomenon. In some the pain would become more localized whilst in others it disappeared from one muscle only to affect another. If the pain had originated in the diaphragm it rarely moved away, although pain from other muscles frequently moved to the diaphragm as the illness progressed. In other words, the disease had a particular affinity for the diaphragm.

Physical signs.—The affected muscles were generally tender on palpation, and when the diaphragm was involved, there was often a protective spasm of the muscles of the abdominal wall, varying in degree from a slight increase in tone to a board-like rigidity reminiscent of a perforated duodenal ulcer.

Swelling of the affected muscles has been described by Sylvest (1934) and Tidy (1951) but, although I looked carefully, I failed to demonstrate it in any of my cases.

Pathology and virology.—Bornholm disease is caused by the Coxsackie Group B of viruses of which there are several types. The Swansea outbreak in 1956 was caused by Type III but I have since found Type I in 2 cases in 1957.

The pathological changes found in the voluntary muscles of suckling mice were described by Dalldorf and Sickles (1948) but it was Lépine *et al.* (1952) who first demonstrated similar changes in an infected human muscle. He wrote: "During the course of the Bornholm disease, the human muscle, in the areas affected by myalgia, presents lesions of inflammatory infiltration and changes in the muscular fibres with hyaline degeneration and fragmentation, reproducing the whole nature of the lesions caused by the Coxsackie virus in the mouse."

Treatment.—There is no specific treatment. Bed rest is indicated in all cases and analgesics administered for pain.

Summary.—The myalgia, which is mainly costodiaphragmatic in distribution, is of sudden onset, severe in degree, has a tendency to migrate, and shows a characteristic tendency to have periods of remissions and exacerbations.

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The following papers were also read:

Electronic Devices.—Dr. D. G. French (*see Practitioner*, 1959, **182**, 231).

Varicose Veins.—Dr. Mark Bradford.

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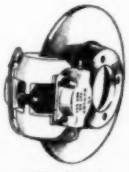

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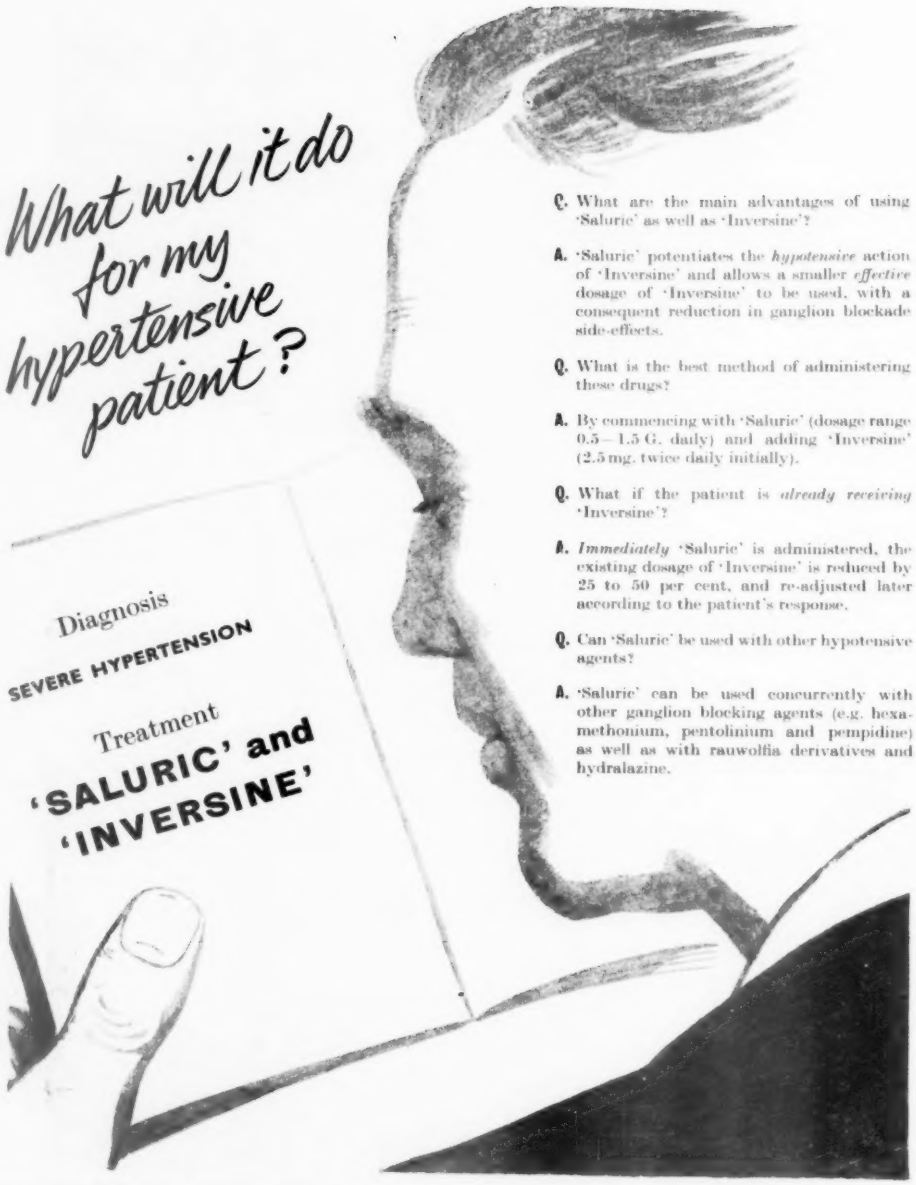

Diagnosis

SEVERE HYPERTENSION

Treatment

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Q. What are the main advantages of using 'Saluric' as well as 'Inversine'?

A. 'Saluric' potentiates the *hypotensive* action of 'Inversine' and allows a smaller *effective* dosage of 'Inversine' to be used, with a consequent reduction in ganglion blockade side-effects.

Q. What is the best method of administering these drugs?

A. By commencing with 'Saluric' (dosage range 0.5—1.5 G. daily) and adding 'Inversine' (2.5 mg. twice daily initially).

Q. What if the patient is *already receiving* 'Inversine'?

A. *Immediately* 'Saluric' is administered, the existing dosage of 'Inversine' is reduced by 25 to 50 per cent, and re-adjusted later according to the patient's response.

Q. Can 'Saluric' be used with other hypotensive agents?

A. 'Saluric' can be used concurrently with other ganglion blocking agents (e.g. hexamethonium, pentolinium and pempidine) as well as with rauwolfia derivatives and hydralazine.

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Clinical Section

President—Sir ERIC RICHES, M.C., M.S., F.R.C.S.

Meeting
February 13, 1959

MEETING HELD AT THE ROYAL NORTHERN HOSPITAL, LONDON

Carcinomatous Neuropathy.—E. C. O. JEWESBURY, D.M., F.R.C.P.

Mrs. H. S., aged 56, first complained of numbness and discomfort in her hands and feet in July 1958. She became unsteady, had several falls, and in October was able to walk only with a stick. Power remained good at first but she was inco-ordinate, especially on the right side, and there was peripheral sensory loss in the limbs, with loss of reflexes. Plantar responses became extensor. Nystagmus was also noted. On November 5 an epileptic attack occurred.

Lumbar puncture (2.12.58) showed colourless C.S.F. (pressure 210 mm.) containing 49 cells per c.mm. (mainly lymphocytes) and 140 mg. protein per 100 ml. Lange curve=5542110000, W.R. negative.

Carcinomatous neuropathy with primary neoplasm of lung was tentatively diagnosed, though there was no conclusive evidence of bronchial carcinoma in the original chest films and there were no symptoms or signs relevant to the chest. Bronchoscopy was also negative. Later films suggested the presence of a rounded opacity in the right lower zone and tomography (17.12.58) confirmed this.

Right lower lobectomy (Mr. Michael Bates) 6.1.59.—Growth (anaplastic carcinoma of oat cell type) involved the right lower lobe and paraœsophageal glands. Has made good progress since operation. She still has nystagmus, marked peripheral neuropathy and extensor plantar responses. She had lost the pain in the limbs before operation. She was then unable to move lower limbs at all but there has been some recovery of movement, particularly of the left leg.

Pharyngeal Pouch.—IAN ROBIN, F.R.C.S.

W. C., male, aged 70.

History.—The patient presented with two months' dysphagia for solids and one week's regurgitation of fluids through the nose. The laryngopharynx was filled with mucus. A barium meal showed a large pharyngeal pouch.

It was proposed to treat the pouch by endoscopic division of the neck of the sac by the method devised by Professor Dohlman of Lund, Sweden. In spite of the acknowledged success of total resection by open operation technique we chose this method because of the frailty of the patient, the large size of the sac, and the many recent successes of the endoscopic method.

(The Dohlman instruments were displayed, together with the modification by Mr. John F. Simpson.)

ADDENDUM.—Operation by the endoscopic method was performed on 19.2.59. The patient left hospital six days later "delighted" with the result, and swallowing without difficulty or discomfort.

REFERENCE

DOHLMAN, G., and MATTSSON, O. (1959) *Amer. J. Roentgenol.*, **81,** 561.

Painful Enteromegaly of Unknown Ætiology.—R. S. MURLEY, M.S., F.R.C.S.

Miss M. F. B., aged 50, first seen by Dr. Raymond Greene on 30.6.58.

History.—June 1956: Onset of severe epigastric pain twice weekly at first but almost daily after January 1958. The pain came on at any time but more often at night. Some relief with analgesics and vomiting. No relation to food and she sometimes ate a good meal immediately after vomiting. Bowels regular and stools normal. Steady weight loss from 157 to 137 lb.

Previous history.—1946: Left hemiparesis and transient diplopia. Multiple sclerosis diagnosed. Little change since then.

1950: Radium menopause for menorrhagia. Subject to migraine for many years. First started with menarche when aged 17 and then eased off for a few years but returned with increasing severity and frequency after 1948.

On examination.—Sallow woman. Tongue normal. Blood pressure 150/100. No abnormality on abdominal and pelvic examination. Sigmoidoscopy normal. Nervous system: Slight internal squint right eye. Optic discs pale. Slight incoordination left arm. Abdominal reflexes absent. Deep reflexes brisker in left lower limb than right. Bilateral extensor plantar response.

Initial investigations.—Hb 108%. E.S.R.

22 mm. in one hour (Westergren). W.B.C. 7,000, differential count normal. Chest X-ray normal.

Barium meal and follow-through (Dr. L. S. Carstairs): Normal œsophagus and stomach. Gross enlargement of duodenal loop and normal emptying at first. Brisk jejunal peristalsis at two hours followed by dilatation of jejunum and regurgitation into stomach. Terminal ileum and colon normal. Conclusions: subacute small gut obstruction.

Referred for surgical opinion on day of barium meal. Palms then were unusually red and she said they sometimes looked as though she had been peeling beetroot. Liver function tests normal. No 5-hydroxytryptamine or 5-hydroxyindole acetic acid in the urine.

The presumptive diagnosis was that of small gut tumour and exploration was advised.

Operation (25.7.58). — Right paramedian incision. Unusually large gall bladder emptying readily on pressure. Dilated pylorus and hugely dilated duodenum about 7·5 cm. diameter. First 4 ft. (120 cm.) of jejunum of similar calibre and thickened with gradual return to normal dimensions about middle of small gut. Terminal ileum and colon normal with ascending colon mesentery. No tumour or organic obstruction. Full thickness biopsy of upper (dilated) jejunum and lower (apparently normal) ileum and appendicectomy.

Histology (Dr. P. M. Peters).—Both gut biopsies show severe œdema of the muscularis with fragmentation and degeneration of some fibres. Diffuse mixed inflammatory cell infiltration including a good number of eosinophils. These changes involve both muscle layers and are more marked in the jejunal biopsy. The mucosa also shows some chronic inflammatory cell infiltration with eosinophils present.

Subsequent investigations.—(1) Repeat barium meal and follow-through (23.12.58): Little change in appearances but no jejuno-duodenal regurgitation seen on this occasion. Severe headache occurred during the examination and was relieved by an anti-histamine.

(2) Barium enema (12.1.59): No abnormality in colon. Tone and activity normal.

(3) Vitamin A absorption test: Plasma level 33 i.u./100 ml. four hours after 350,000 i.u. vitamin A by mouth. Repeat test two weeks later showed plasma level 100 i.u./100 ml. after four hours (normal not less than 500 i.u./100 ml. at four hours).

(4) Stools: No parasites, ova or cysts present. Fæcal fat 19·1 grams; split fat 15·3 grams and unsplit fat 3·8 grams/100 grams dry weight (total fat high normal).

(5) Other investigations: Liver function tests included thymol, ammonium sulphate and zinc sulphate turbidity; serum glutamine pyruvate transaminase; bromsulphthalein and serum protein estimations; all of these were normal. Serum alkaline phosphatase 17 K.A. units. Glucose tolerance and serum calcium normal.

Progress.—Following operation the patient declared that she was greatly improved though it had been made quite plain to her that no curative steps had been taken. Only three attacks of abdominal pain occurred in the next seven months by comparison with almost daily attacks beforehand.

Comment.—The ætiology of this case remains obscure. It is difficult to relate the gut changes to the patient's apparently non-progressive multiple sclerosis or to her migraine of long standing. Although delayed emptying of the stomach and gall bladder has been described by Carstairs (1958) in people with migraine, we are not aware of histological changes in the gut having been reported.

It is tempting to suggest that the gut disorder may be allergic, but there is no evidence of this and the patient showed no hypersensitivity to routine allergen tests.

It should be emphasized that the tissue changes in this case are more marked in the muscular than the mucosal layers and are not confined to the dilated and thickened part of the gut. The impaired fat absorption is presumed to be secondary to the gut changes. A preliminary search of the literature and discussion with colleagues have brought no similar cases to light.

REFERENCE

CARSTAIRS, L. S. (1958) *Proc. R. Soc. Med.*, **51**, 790.

Intracerebral Hæmorrhage and Brain-stem Compression Treated Initially by Hypotension and Later by Evacuation of the Hæmatoma.—D. CROOKE MORGAN, M.B. (for LESLIE OLIVER, F.R.C.S., F.A.C.S.).

Mrs. L. S., aged 54, was admitted to hospital in coma on 16.6.58 after a sudden severe headache followed rapidly by unconsciousness.

On examination.—Comatose but responding to painful stimuli. Gross neck stiffness; constriction of the right pupil; hypotonia of the left arm and leg; diminished tendon reflexes on the left; and a positive Babinski sign on both sides.

Investigations.—Lumbar puncture: Uniformly

blood-stained fluid. X-ray of skull: Pineal gland displaced to the left. Right carotid angiogram: A–P views, displacement of the anterior cerebral artery to the left and elevation of the middle cerebral artery; lateral views, stretching of the carotid "siphon" and upward curving of the middle cerebral artery.

After these investigations, her condition deteriorated: there was no response to painful stimuli; both pupils were fixed and dilated; there was Cheyne-Stokes breathing, a rapid irregular pulse, a temperature of 101° F., flaccidity of all limbs and a positive Babinski sign on both sides.

Diagnosis.—Spontaneous hæmatoma in the right temporal lobe, subarachnoid hæmorrhage, and advanced brain-stem compression.

Management.—As she was *in extremis*, it was decided to produce shrinkage of the brain by cooling and thereby reduce brain-stem compression. Surface cooling by means of ice-bags and fans was used in combination with intravenous injections of pethidine, chlorpromazine and promethazine. The rectal temperature was maintained in the region of 87° F. for thirty-six hours. At the end of this time, the level of consciousness had improved; breathing was regular; the pulse was slower and regular, and the right plantar reflex was normal.

After tracheostomy, the opportunity was seized to elevate a bone flap and evacuate the intracerebral hæmatoma. The temperature was then allowed to rise gradually. A sharp fall in blood pressure was corrected by intravenous injections of hydrocortisone. By 25.6.58 consciousness was fully restored but there was a left hemiparesis, which, however, recovered by the time the patient was discharged from hospital on 21.8.58.

Comment.—This case illustrates an important application of induced hypothermia. By shrinking the brain in this way a very advanced degree of brain-stem compression was improved enough to allow evacuation of the hæmatoma.

Animal experiments show that during recovery from operations performed during induced hypothermia the secretion of the adrenal cortex is three to four times that following operations performed at normal temperatures (MacPhee *et al.*, 1958). Adrenal insufficiency was therefore the likely explanation of this patient's hypotension and its response to hydrocortisone.

REFERENCE

MACPHEE, I. W., GRAY, I. C., and DAVIES, S. (1958) *Lancet*, ii, 1196.

Combined Medical and Surgical Treatment of Obesity.—PATRICK CLARKSON, M.B., F.R.C.S., and RAYMOND GREENE, D.M., F.R.C.P.

History.—This 42-year-old man, after scarlet fever at the age of 5, started gaining weight at the rate of about 1 st. per year until he was 18 years old, after which his weight varied between 20 st. and 24 st. Under medical treatment this was reduced to 18 st. This treatment consisted in the provision of an adequate calorie intake obtained almost entirely from protein, which was unrestricted. He was allowed reasonable amounts of fat and fried food was not denied him, for any reasonable person would rather be obese than exist on a fat-free diet. Experience shows that the appetite does not demand much fat if carbohydrate is greatly restricted. His carbohydrate intake was reduced to the lowest practicable level.

He was referred for surgical treatment of his abdominal "apron" and of his gynæcomastia, when his weight was 17 st.

It seemed clear that three of the five direct indications for surgery in obesity were present in this case. That is, he had bulky and dependent breasts, a heavy abdominal "apron", and a "lost penis" invaginated in a pre-pubic pad. The fourth indication for surgery in obesity is intertrigo between grossly enlarged thighs, which may be so severe and so otherwise intractable as to render the patient largely bedridden. The fifth indication is lipodystrophy of which the mechanical effects or unsightliness may only respond to surgical excision.

Operation (6.11.58, at the Royal Northern Hospital).—The excess fat from each bosom (about 1½–2 lb.) was removed and a male contour restored. Under the same anæsthetic a radical removal of the abdominal apron was done, preserving the umbilicus. The removal included most of the pre-pubic pad which uncovered the penis.

Healing was relatively uneventful and he was discharged after three weeks.

The total weight of skin and fat removed was about 14 lb. His weight on discharge was 16 st., and at present (three months later) is about half a stone less. He has been dieting since operation.

Comment.—It is interesting to consider the maximum weight of fat which can be removed at one operation. I (P. C.) have never removed more than about a stone at one operation. I have sometimes removed as much as this both from the abdomen or from both breasts. It is mainly the relief of the mechanical impediment

(including the intertrigo and other disadvantages) and of the unsightliness that is effected by surgery, but the weight loss can be generally beneficial, especially in relieving dyspnœa after radical breast reductions.

When operations for obesity are confined to the five indications listed here recurrence, in our experience, has not occurred—without gross over-eating. This is probably because it is not merely fat which is removed, but adipose tissue, the store room for fat. Without the scaffolding fat can no longer be stored in that situation, though it may still increase in other places. The fact that the patient continues to lose weight on a normal diet may be attributed to the increase in the output of energy which the operation has made possible.

Radioactive Phosphorus Uptake as a Guide to Radiotherapy for Superficial Malignant Melanomata.—ANTHONY GREEN, F.R.C.S.

Radioactive phosphorus injected intravenously is absorbed in the active metabolism of the cell, especially in the D.N.A. of the nucleus.

Before this test could be used certain fundamentals were checked. A patient suffering from an advanced and ulcerating breast carcinoma was given an intravenous injection of radioactive phosphorus, and surface beta ray counting was done. High readings were obtained in the active malignant section, medium readings in the section with moderate quantity of cancer cells, and low readings where there was no malignancy. The above was confirmed by histological section underneath the counted area, and by autoradiographs. This showed that the phosphorus was concentrated in the malignant section.

Two elderly patients with malignant melanoma of the thumb were given 50 microcuries intravenously before treatment and a dose of X-rays (1,000 r) was repeated to a total dose of 5,000 to 7,000 r in 5 to 10 weeks. During this time, the repeated tests for the uptake of phosphorus in the tumour showed a decline, and the dose was stopped when the uptake showed no abnormal elevation. These cases have been well for over two years.

Another successful case was mentioned with a malignant melanoma of the neck, with a large gland in the upper cervical region. The skin and gland were enclosed in a uniform field of irradiation and the skin uptake was used as an index of the treatment of the gland. Mention was made of the value of this in the differential diagnosis of difficult brown stains and hæmatoma and proof was offered that a low reading meant no malignancy. It was emphasized that the clinical range for the measurement of the beta rays of phosphorus from a tumour was approximately 5 mm.

The following cases were also shown:

Two Unusual Causes of Epistaxis; I. Familial Hereditary Telangiectasia (Osler's Disease). II. "Bleeding Polypus" of Nasal Septum.—Mr. J. C. BALLANTYNE.

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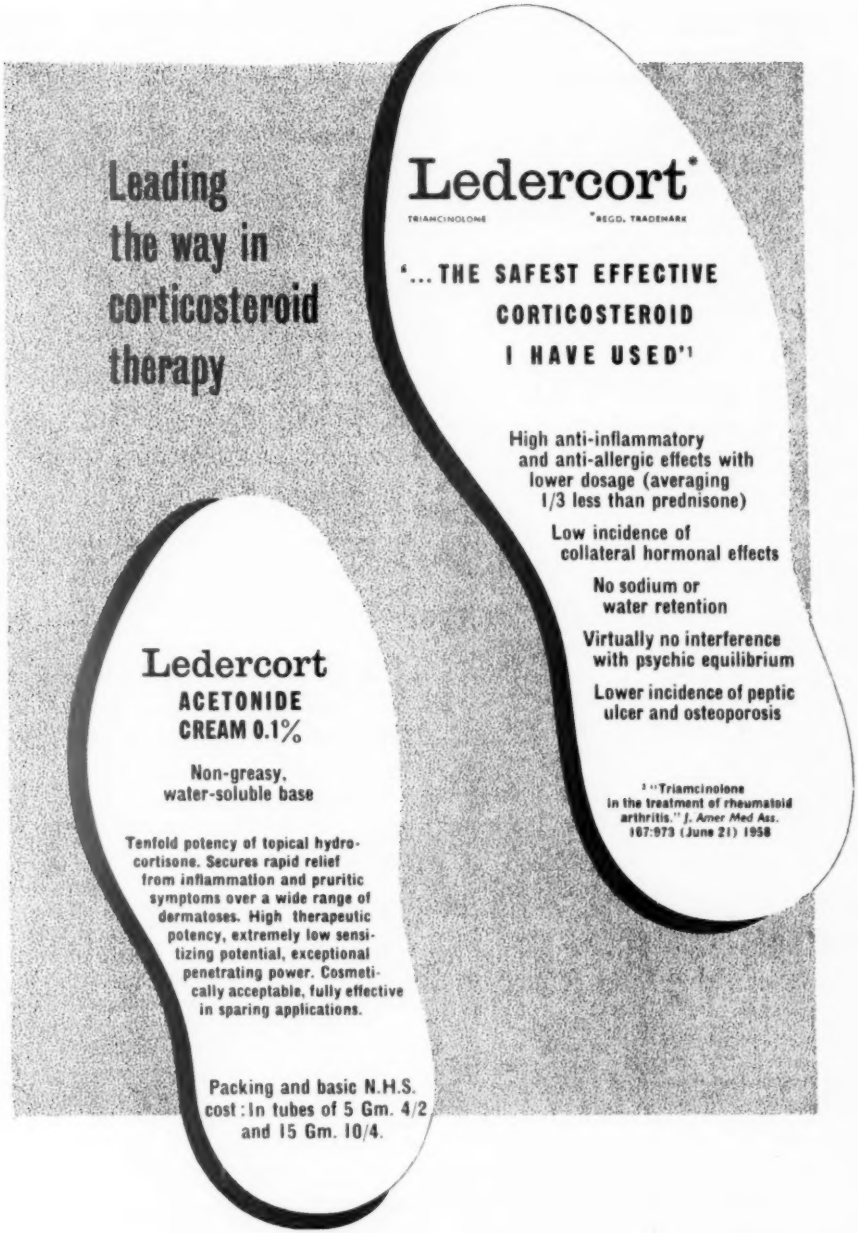
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BOOK REVIEWS

Carcinoma of the Lung. Edited by J. R. Bignall, M.D., M.R.C.P. Vol. I of Monographs on Neoplastic Disease at Various Sites; General Editor: D. W. Smithers, M.D., F.R.C.P., F.F.R. (Pp. xii+298; illustrated. 55s.) Edinburgh and London: E. & S. Livingstone Ltd. 1958.

This is the first of a series of monographs on neoplasm at individual sites. The scope of the series as outlined by Professor Smithers in his general introduction is wide, and embraces all important aspects of the subject. This, the first volume, is concerned with carcinoma of the lung and is the work of Dr. Bignall and seven other contributors who, between them, deal with statistics, causation, pathology, clinical features and treatment of the disease. The material is extensive, and much information has been assembled which is not easily accessible to the general reader. It has been presented in a concise and readable form. In some portions of the book, notably on the spread of carcinoma and the use of irradiated gold grains implanted into the tumour at operation, some original work has been documented. The book has been excellently produced, and the illustrations throughout are of a high quality. It will be of value to all those interested in this subject, and has set a high standard for the succeeding volumes.

Tumours of the Bladder. Edited by David M. Wallace, O.B.E., M.S., F.R.C.S. Vol. II of Monographs on Neoplastic Disease at Various Sites; General Editor: D. W. Smithers, M.D., F.R.C.P., F.F.R. (Pp. xvi+352; illustrated. 60s.) Edinburgh and London: E. & S. Livingstone Ltd. 1959.

This is an excellent book. It is easy to read, it gives the best and most up-to-date account of the subject and it is well illustrated.

After this eulogy it is perhaps ungenerous to criticise, but there are several criticisms. There is some repetition and, although it is informative, too much space is devoted to statistical matters. The reviewer believes that more prominence should be given to the value of the excretory urogram in staging of bladder tumours; he considers that this gives more accurate information than does bimanual pelvic examination. The value of cytology in the control of industrial carcinoma of the bladder is accepted, but not enough credit is given to it as a method of grading tumours of the bladder.

The reviewer doubts whether a case has been made for obtaining a piece of the tumour for biopsy in every instance; he believes that clinical assessment assisted by cytology and the histology of fragments obtained by simpler methods allows of assessment that is nearly as accurate as that afforded by biopsy, and is safer for the average surgeon, although the methods advocated may be better for the expert. Much is made of the risk of implanting tumour cells in epithelium that has been damaged by cystoscopy, but this risk must be slight, because during the past twelve years the reviewer has removed at least 50 prostates whilst dealing with tumours of the bladder by open cystotomy, and has not seen a single case of implant of the tumour into the prostatic cavity. Whilst the danger of implantation by this method is stressed, one is advised to explore the extraperitoneal perivesical space with the finger, so that the growth can be palpated both on its outer surface and also between a finger within the bladder and a finger without the bladder to assess the degree of infiltration and thickness, a procedure that might be more dangerous and more likely to disseminate the disease than other methods that are condemned. Again, although it is obvious from charts showing results of treatment that combined assaults are made on the tumour by several methods, yet very little is said in the text about the fact that a combination of treatments, or repeated treatments by different methods may be necessary for many tumours, provided the total dose of irradiation is kept within safe limits.

Despite these criticisms, the reviewer thoroughly recommends the book.

The History and Philosophy of Knowledge of the Brain and its Functions. An Anglo-American Symposium, London, July 15–17, 1957. Edited by F. N. L. Poynter, Ph.D., F.L.A. (Pp. x+272; illustrated. 22s. 6d.) Oxford: Blackwell Scientific Publications. 1958.

This volume contains sixteen of the contributions presented before this important Symposium which preceded the 1st International Congress of Neurological Sciences. The first session was devoted to the concepts of brain function in antiquity, the contributors being W. Penfield, D. H. M. Woollam, J. S. Wilkie and Ilza Veith. The second session had mostly to do with ideas of consciousness with papers by Denis Williams and Sir Russell Brain and one by Macdonald

Critchley on the origin of language. The particular contributions of the mediæval and Renaissance authors to our understanding of the brain constituted the third session with communications by W. Paget, W. Riese and W. P. D. Wightman, while at the fourth session E. H Ackerknecht, A. Lewis and H. McIlwain dealt with progress in the nineteenth century with reference to Gall and the phrenologists, J. C. Reil and the chemists respectively. The final session was concerned with concepts of cortical activity, the contributors being Mary A. B. Brazier, Sir Francis Walshe and Chandler McC. Brooks.

The volume ends with a charming address by Sir Henry Dale, setting forth the importance of Anglo-American co-operation in science and medicine. This address will be treasured, not only because of the universal affection in which this venerable author is held, but because it contains so many of his own experiences.

To have these interesting chapters on the history of our knowledge of the brain collected into one volume is a privilege as well as a convenience.

Poliomyelitis. Papers and Discussions presented at the Fourth International Poliomyelitis Conference. Compiled and edited for the International Poliomyelitis Congress. (Pp. xviii+684; illustrated. 60s.) Philadelphia and Montreal: J. B. Lippincott Company. London: Pitman Medical Publishing Co. Ltd. 1958.

The Third International Poliomyelitis Congress in 1954 preceded the Francis Report of the field trial of Salk vaccine in North America, whereas the Fourth Congress at Geneva in 1957 was separated by two years from the startling events which occurred shortly after this first demonstration of effectiveness and the subsequent widespread introduction of vaccination in the summer of 1955. In the intervening period means had been found to ensure safety of the vaccine, and many countries beside America had experience of its manufacture and use. Particular interest at Geneva centred therefore on the problem of ensuring consistent potency in commercial batches, and in finding the method of administration which would give most durable immunity. Another major topic was the research on attenuated virus vaccines, and a comparison between the immunity thus conferred with that given by inactivated virus vaccines of the Salk type. The optimistic hopes, expressed editorially, for the rapid elimination of poliomyelitis by vaccination were not realized in 1958, but this does not detract from the high quality of the papers and discussions reported in this volume.

A large part of the Congress's work was concerned with other topics in poliomyelitis and related fields—the ECHO and Coxsackie viruses causing abacterial meningitis, problems of diagnosis, general considerations of tissue culture and viruses, the management of poliomyelitis with particular reference to respiratory distress and severe orthopædic disability. All these discussions are fully reported, with a high standard of tabular material and illustration, and some outstanding reproductions of photomicrographs. Although a slip has occurred in the layout of the filtration method column of Table 23 to Bodian's paper, the volume is otherwise commendably free from typographical errors.

Cell and Tissue Culture. By John Paul, M.B., Ch.B., Ph.D., M.R.C.P.Ed. (Pp. viii+261; illustrated. 30s.) Edinburgh and London: E. & S. Livingstone Ltd. 1959.

This is an excellent and entirely practical textbook. The technique of cell culture has passed out of the hands of pioneers and experts and is now in everyday use by virologists, biochemists and even routine diagnostic laboratories. The "know-how" is often only available from mouth to mouth, and in few other sciences is success so easy when essentials are known and failure so certain when they are not.

The reviewer has already profited greatly from suggestions in nearly every chapter, and the book is as necessary to the experienced worker as to the beginner. Bibliography is full and up to date, and illustrations numerous and good. Most of us will only be sorry that so satisfactory a guide was not available years ago.

Medical Laboratory Investigations. Their Use and Interpretation. By Ian Dawson, M.A., M.D., M.R.C.P., and William Goldie, M.A., M.B., F.R.C.P., F.R.C.P.(E). (Pp. xv+260; 35s.) London: Butterworth & Co. (Publishers) Ltd. 1958.

It is stated in the introduction to this book that it is intended "to provide the clinician, the family doctor, the registrar and house physician or surgeon and the medical student with information about which laboratory investigations will help them most, what sort of material the laboratory needs, how accurate the investigations are, what the principal sources of error are, and what the results mean". An examination of the book shows how little of the authors' aims has been attained, for the whole tone of the book appears superficial. It is therefore difficult to recommend it as it stands.

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Textbook of Medical Treatment. Edited by D. M. Dunlop, B.A.(Oxon), M.D., F.R.C.P.Ed., F.R.C.P.Lond., Sir Stanley Davidson, B.A.(Camb.), M.D., F.R.C.P.Ed., F.R.C.P.Lond., M.D.(Oslo), S. Alstead, M.D., F.R.C.P.Ed., F.R.C.P.Lond., P.R.F.P.S. 7th ed. (Pp. xix+924; 55s.) Edinburgh and London: E. & S. Livingstone Ltd. 1958.

This well-known textbook from the Scottish Schools of Medicine has now reached its 7th edition but this time Dr. Stanley Alstead has taken the place of Sir John McNee; and the three main editors have been assisted by a team of twenty-two experts who have been responsible for different portions of the book.

The general form has followed that of previous editions and each subject commences with a short résumé of the disease after which the treatment follows automatically. Careful perusal by the reviewer confirms the excellent nature of the information provided, and the medical care of the various conditions described is detailed and on common-sense lines in accordance with present British medical practice. The inclusion as a glossary of the approved names of drugs followed by their proprietary preparations is a welcome new feature as is the short chapter on the general principles underlying prescribing in general. This book should be on the bookshelf of every physician whether he be a consultant or in general practice.

Aids to Medical Treatment. By T. H. Crozier, B.Sc., M.D., D.P.H., F.R.C.P. 4th ed. (Pp. 367; 15s.) London: Baillière, Tindall & Cox. 1959.

There are now more than forty volumes in this series, and that on medical treatment must be one of the most difficult to write and to keep up to date. Special subjects, such as dietetics and dermatology, have been relegated elsewhere, and there is nothing here, rather surprisingly, on neurosis or psychosis; but, after an introduction to antibiotics, Dr. Crozier has gone systematically over the various organs, and has included chapters on infectious, metabolic and tropical disease, and on intestinal parasites, physical and chemical agents, and vitamin deficiencies. There are valuable summaries on the effects of radioactivity, the varieties of insulin, ACTH and cortisone, water and electrolyte depletion, ganglion blocking agents and anticoagulants, and on the chemotherapy of pulmonary tuberculosis.

The side-effects of various drugs are frequently noted, and it is most helpful to have given the names and makers of proprietary preparations in addition to more formal nomenclature. It would surely be an advantage to the student to expand the index considerably; at present such words as "antihistamines", "ataractics", and "tranquillizers" find no place therein, and many drugs, though frequently mentioned in the text, are omitted from the last five pages.

Shakespeare and Medicine. By R. R. Simpson, M.B., Ch.B., F.R.C.S., F.R.C.S.Ed. (Pp. vi+267; 25s.) Edinburgh and London: E. & S. Livingstone Ltd. 1959.

The medical references in Shakespeare are of interest to doctors who will certainly find this book of value both for reading and reference. The author has collected and classified 712 medical references in the plays and poems and has added many illuminating notes and explanations. Many of the chapters are complete essays in themselves and were intended in the first instance for lectures to medical societies; this has led to a certain amount of unavoidable overlapping and repetition. The author mentions J. C. Bucknill's book on "The Medical Knowledge of Shakespeare" (1860) but makes no special reference to the same author's "The Psychology of Shakespeare" (1859).

There is an extremely interesting chapter devoted to a discussion as to what influence, if any, Shakespeare's son-in-law Dr. John Hall may have had on the writings. It is noted that no doctor appears as a character in a play written before 1600, and the original conclusion is reached that "while there is no evidence that Hall influenced the medical references . . . there is some evidence to suggest that in the portrayal of doctors as doctors in the plays, Shakespeare might have been influenced by the character and qualities of his own doctor son-in-law".

The text of the book is enlivened by some bold and stimulating criticisms of the views held by some well-known authorities. We think that many doctors and laymen will wish to have "Shakespeare and Medicine" on their shelves.

The Pathology and Management of Portal Hypertension. By R. Milnes Walker, M.S., F.R.C.S. (Pp. vii+113; illustrated. 35s.) London: Edward Arnold (Publishers) Ltd. 1959.

The author has given an account of portal hypertension based on a personal series of 200 patients, consequently he can and does speak with authority on this subject. This monograph is rather too brief to allow the author to complete his declared task of providing a guide to physicians and to stimulate further research. Physicians will derive much benefit from reading this book but detailed guidance is lacking. Similarly the research worker will be disappointed that Professor Milnes Walker did not give a longer

account of the disordered physiology of portal hypertension, which with all the author's experience would have been so valuable.

For the surgical tyro this book is excellent, it gives him the information he needs in an extremely palatable form.

Clinical Neurophysiology. By John Marshall, M.D., F.R.C.P.(Ed.), M.R.C.P., D.P.M. (Lond.). (Pp. viii+296; illustrated. 37s. 6d.) Oxford: Blackwell Scientific Publications. 1959.

The amount of literature published on the subject of neurophysiology both in the shape of books and of journals is enormous. A large proportion of the material it contains is at any one moment of only academic interest to the clinician. That which has an immediate application to clinical work represents only about one in a thousand of the volume and is bewilderingly difficult to trace without the help of big-hearted physiologists. Yet this tenuous fraction holds the key to the understanding of many a phenomenon encountered in neurological practice, and provides the basis of new methods of investigation.

Dr. Marshall has done a great service to neurology and allied subjects by extracting from this welter of material that which is of value and relevant, and publishing it in an easily understandable form in a volume of 296 pages. Few neurologists, budding or withering, would claim that they would not be more skilled for a better understanding of the fund of knowledge brought together between its covers: and in the case of students of neurological disorders it should constitute a "must".

The only criticism one could level against this thesaurus of useful knowledge is that an additional paragraph to elaborate a point here and there might conduce to easier assimilation.

International Journal of Radiation Biology. Editor: W. M. Dale, M.D., D.Sc. Vol. I, No. 1 (Pp. 104; illustrated. £1 0s. per part; £3 15s. per vol. (4 issues)). London: Taylor & Francis, Ltd. 1959.

The field of experimental and applied radiation biology has widened considerably during the past few years. The publication of this new international journal will be welcomed by all who are engaged in radiobiological research, because it will provide an additional outlet for the diverse investigations, now pursued throughout the world. According to the Editor, the journal will publish besides original contributions, brief articles and reviews of books, brief summaries of proceedings and symposia pertinent to radiobiology. Review articles dealing with topics of special interest are also contemplated. The Editor is supported in his task by an international Editorial Board. The first issue of the Journal well illustrates its international character; it contains contributions from Holland, Germany, India, Italy and Norway besides those from Great Britain. Each contribution has besides English, summaries in German and French. There are two well-written reports, one on the First International Congress of Radiation Research, held in Vermont, U.S.A. (August 1958) and another on the European Conference on the use of ionizing radiations for food preservation held in Harwell (November 1958). The summaries of some of the important contributions of these conferences will have interest for those in the medical profession. The printing and illustrations of the new Journal are of very high quality.

A Short Practice of Surgery. By Hamilton Bailey, F.R.C.S.(Eng.), F.A.C.S., F.I.C.S., F.R.S.E., and McNeill Love, M.S.(Lond.), F.R.C.S.(Eng.), F.I.C.S. 11th ed. (Pp. xii+1389; illustrated. £4 4s.) London: H. K. Lewis & Co. Ltd. 1959.

This textbook of surgery has now been appearing in successive editions for a little over a quarter of a century and has retained throughout all these years its great popularity with students. This is not surprising when one looks at the new eleventh edition which has just been published.

The book appears in its unusual but attractive pale canvas covered boards. The paper throughout is glazed and on it appear a multitude of illustrations both in black and white and colour which bring home to the reader information which the printed word often fails to do. The authors have been joined by three others: Charnley, Cleland and Knight, who have added accounts of their own specialties but have kept to a style very similar to that found in the rest of the volume.

The book is splendidly up to date and the only criticism is that the style, being essentially didactic, leaves no room for second thoughts on any subject and perhaps rather artificially shuts off medical aspects of many diseases. On the other hand students like nothing better than to be told clearly and precisely the reason for everything, even if it is not the whole story. The standard of workmanship throughout this volume remains exceptionally high. The little footnotes about physicians and surgeons are an attractive addition. Finally, at four guineas the book represents incredibly good value in these days of mounting prices.

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This is a Reception Hospital in detached grounds with a separate entrance, to which patients can be admitted. It is equipped with all the apparatus for the complete investigation and treatment of Mental and Nervous Disorders by the most modern methods: insulin treatment is available for suitable cases. It contains special departments for Hydrotherapy by various methods, including Turkish and Russian Baths, the prolonged immersion bath, Vichy Douche, Scotch Douche, Electrical baths, Plombiere's treatment, etc. There is an Operating Theatre, a Dental Surgery, an X-ray Room, an Ultra-Violet Apparatus, and a Department for Diathermy and High-Frequency treatment. It also contains Laboratories for Biochemical, Bacteriological and Pathological Research. Psycho-therapeutic treatment is employed when indicated.

MOULTON PARK

Two miles from the main Hospital there are several branch establishments and villas situated in a park and farm of 650 acres. Milk, meat, fruit and vegetables are supplied to the Hospital from the farm, gardens and orchards of Moulton Park. Occupational Therapy is a feature of this Branch, and patients are given every facility for occupying themselves in farming, gardening and fruit growing.

BRYN-Y-NEUADD HALL

The seaside house of St. Andrew's Hospital is beautifully situated in a park of 330 acres, at Llanfairfechan, amidst the finest scenery in North Wales. On the north-west side of the Estate a mile of sea-coast forms the boundary. Patients may visit this branch for a short seaside change or for longer periods. The Hospital has its own private bathing house on the seashore. There is trout-fishing in the park.

At all the branches of the Hospital there are cricket grounds, football and hockey grounds, lawn tennis courts (grass and hard courts), croquet grounds, golf courses, and bowling greens. Ladies and gentlemen have their own gardens, and facilities are provided for handicrafts, such as carpentry, etc.

For terms and further particulars apply to the Medical Superintendent: TELEPHONE No. 4354 Northampton (three lines) who can be seen in London by appointment.

Have you received your copy of

MODERN CONTRACEPTIVE TECHNIQUE?

This manual on contraception has already proved invaluable to doctors in advising their patients. It presents a concise and compact survey of methods commonly used, together with notes on methods which have medical approval, and also on others which are contra-indicated. You are invited to write for your copy now.

The case against "natural" methods

Unreliable and harmful methods of contraception, such as "coitus interruptus", are chiefly used because of the slight loss of sensitivity experienced with protectives (condoms). This problem is now largely overcome by Durex Gossamer, a new type of *lubricated* protective, which increases the level of sensitivity. The lubricant, called "Sensitol", is not "wet or messy". *Samples on request.*

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in Hospitals

Infection from bedclothes has always been an item of concern in Hospitals. Until recently the most satisfactory method was to wash the blankets in a suitable detergent, rinse and then treat with a cation-active germicide. The action of cleaning and disinfection can now be carried out *simultaneously* by using the new detergent/sterilizer Hytox, which is effective against a wide range of Gram-positive and Gram-negative organisms.

HYTOX

THE COMBINED DETERGENT/STERILIZER

Extract from letter to "The Lancet" 11.10.58

. . . Hytox has now been tried at one of our Hospitals with great success. The blankets emerged very white, soft and clean and the fibres have anti-bacterial properties and are sterile. Hytox is also inactivated by traces of ordinary washing soap in the blanket or in the crevices of the washing machine; so the first time a used blanket is washed the results may be disappointing. However, the second time the blankets are washed in a clean machine the results are very satisfactory.

Write for literature and testing sample to:

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ST. ANDREW'S HOSPITAL

FOR NERVOUS AND MENTAL DISEASES

NORTHAMPTON

President—THE EARL SPENCER

Medical Superintendent—THOMAS TENNENT, M.D., F.R.C.P., D.P.H., D.P.M.

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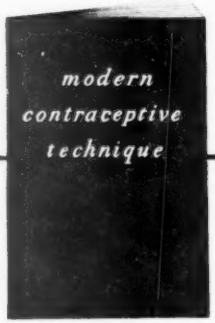

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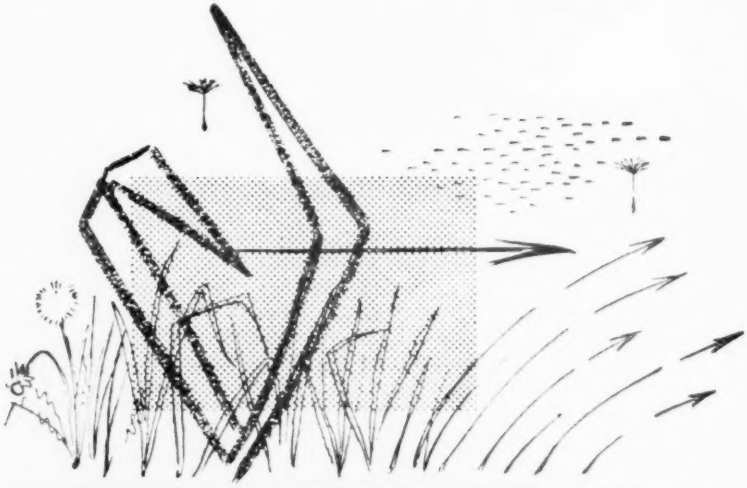
In hay fever and perennial vasomotor rhinitis



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